PROCEEDINGS
OF THE
ROYAL SOCIETY OF MEDICINE
Vol. 49 No. 11 November 1956

CONTENTS

	Whole Proceedings Page
Section of Comparative Medicine. DISCUSSION ON SYNERGY IN CHEMOTHERAPY	871
Section of Endocrinology	
Primary Aldosteronism.—M. D. MILNE, M.D., and R. C. MUEHRCKE, M.D..	883
The Significance of the Assay of Aldosterone in Human Urine and Blood.—O. GARROD, M.D., SYLVIA A. SIMPSON, B.Sc., and J. F. TAIT	885
Some Factors Affecting Aldosterone Secretion.—O. GARROD, M.D., SYLVIA A. SIMPSON, B.Sc., and J. F. TAIT..	888
Malignant Hypertension and Hyperaldosteronism.—C. HOLTEN, M.D., and V. POSBORG PETERSEN, M.D.	890
Section of Urology. DISCUSSION ON UROLOGY IN CHILDREN	891
Section of the History of Medicine	
April 4, 1956. The Management of Lunacy in Seventeenth Century England. An Investigation of Quarter-sessions Records.—A. FESSLER, M.D., L.R.C.P., M.R.C.S.. .	901
June 6, 1956. Miss Florence Nightingale and the Doctors.—President's Address by Sir ZACHARY COPE, M.S., M.D., F.R.C.S.	907
Section of General Practice	
March 21, 1956	
Cord Round the Neck.—C. W. WALKER, M.B.	915
The Care and Treatment of Acne Vulgaris.—Sir WALTER FERGUSSON HANNAY, M.R.C.S., L.R.C.P.	917
The Importance and Proportion of Minor Ailments in General Practice.—BERTHA TURNER, M.D., B.S.	918
Sigmoidoscopy in General Practice.—KENNETH C. HUTCHIN, M.D.	919
Menstrual Histories.—L. CARLYLE LYON, M.B., Ch.B..	921
April 18, 1956. DISCUSSION ON THERAPEUTIC RESEARCH: VIEW OF A GENERAL PRACTITIONER, A UNIVERSITY PROFESSOR AND A PHARMACEUTICAL COMPANY DOCTOR ..	923

Continued overleaf

RIDDOVYDRIN
NASAL OINTMENT

- **Indications: HAYFEVER, NASAL CATARRH, RHINITIS**
- **Remarks:** Rapidly absorbed by the mucous membrane, this nasal ointment quickly reduces inflammation, swelling and secretion caused by pollen toxins, and exercises a powerful antispasmodic action on Hayfever, Hay Asthma sufferers and those with allied respiratory complaints affecting the nasal area.
- **Composition:** Contains Vitamin C in combination with the active constituents of the RIDDOVYDRIN ASTHMA INHALANT, increasing demands of which speak for the benefit derived from these products.

Sole Manufacturers:
RIDDELL PRODUCTS LIMITED
RIDDELL HOUSE, 10-14 DUNBRIDGE STREET, LONDON, E.2
Telephone: BIShopsgate 0843. Telegrams: Pneumostat, Beth, London
BRANCH OFFICE: 11 Mansfield Chambers, St. Ann's Square, Manchester 2

CONTENTS (*continued*)

	Whole Proceedings Page
Clinical Section	
March 9, 1956	
Hæmophilia with Small Bowel Obstruction Due to an Ileal Hæmatoma.—A. G. PARKS, M.Ch., F.R.C.S. (for S. H. WASS, M.S., F.R.C.S.)	933
Polyarteritis Nodosa.—R. C. KING, M.D., M.R.C.P. (for E. R. CULLINAN, M.D., F.R.C.P.)	934
May 11, 1956. MEETING AT ADDENBROOKE'S HOSPITAL, CAMBRIDGE. List of Cases	935
Books Received for Review. Books Recently Presented and Placed in the Society's Library	936, 968
Section of Obstetrics and Gynæcology	
May 25, 1956. Specimens shown	937
June 22, 1956. Prolapse of the Umbilical Cord.—PHILIP RHODES, F.R.C.S., M.R.C.O.G.	937
Section of Pædiatrics. CASES	941-944
Section of Proctology	
May 2, 1956. DISCUSSION ON ILEOSTOMY	945
June 15, 1956. MEETING AT BRISTOL ROYAL INFIRMARY	
Anal Fissure in Pædiatric Practice.—JOHN APLEY, M.D., M.R.C.P.	956
Complete Prolapse of Rectum: Thiersch's Operation.—A. G. MCPHERSON, M.Chir., F.R.C.S.	957
Book Reviews	959
Section of Orthopædics. MEETING AT THE NUFFIELD ORTHOPÆDIC CENTRE, OXFORD	
Blood Supply of the Epiphyseal Plates of the Rabbit's Tibia.—J. D. MORGAN, F.R.C.S.	961
Assessment of Ununited Fractures of the Carpal Scaphoid.—J. H. S. SCOTT, F.R.C.S.	961
Pseudarthrosis of the Hip-joint.—R. G. TAYLOR, M.A., M.Ch., F.R.C.S.	963
Drilling of the Osteoarthritic Hip.—J. AGERHOLM-CHRISTENSEN, D.M.Copenhagen, and J. R. W. GLEAVE, B.M., B.Ch.	964
Structural Deformities of the Outer Third of the Adult Tarsal Navicular.—WILLIAM WAUGH, M.Chir., F.R.C.S.	965

N.B.—The Society does not hold itself in any way responsible for the statements made or the views put forward in the various papers.

Copyright: The Society holds the copyright of all matter accepted for publication in the *Proceedings*. Requests for subsequent publication elsewhere should be made to the Honorary Editors. All papers, &c., presented at meetings (other than those which have been previously published) are held to be subject to the Society's copyright until a decision in regard to their publication has been made.

Towards meeting the demands of growth

THE HIGHER metabolic needs of the young which accompany natural growth and which are further increased by heavy daily expenditure of energy, tend to diminish vital reserves.

'Ovaltine' helps to satisfy the extra needs for proximate and accessory food principles. The malt, milk, cocoa, soya and eggs in 'Ovaltine' are blended to form a highly nutritious food beverage — deliciously flavoured and easily assimilated.

It is of value in helping to maintain normal weight increase and is of undoubted help to those recovering from debilitating effects of common childhood fevers.

For growing children 'Ovaltine' is a dietary reinforcement which can be routinely recommended with confidence.

Vitamin Standardization per oz.—Vitamin B_1, 0·3mg.; Vitamin D, 350 i.u.; Niacin, 2mg.

OVALTINE

A. WANDER LTD.
42 Upper Grosvenor Street,
London W.1.

M.384

Section of Comparative Medicine

President—Professor JAMES MCCUNN, F.R.C.S., L.R.C.P., M.R.C.V.S.

[*April* 18, 1956]

DISCUSSION ON SYNERGY IN CHEMOTHERAPY

Dr. L. G. Goodwin, Wellcome Laboratories of Tropical Medicine, London:

Sulphonamides and Folic Acid Antagonists in Malaria and Toxoplasmosis

For many years the method of selection of new chemotherapeutic substances has been by trial and error. The empirical method is bound to remain of primary importance, but as knowledge of the processes of intermediate metabolism of the host and the parasite accumulates, it becomes possible to predict the chemical structure of substances likely to interfere.

The drug known as pyrimethamine is a good example of this change in the pattern of chemotherapeutic research. The synthesis by the cell of nucleoprotein is essential for its organization and reproduction. Sulphonamides, discovered empirically, are known to interfere at an early stage in this process of synthesis by competing with *p*-aminobenzoate (*p*.AB), which is essential for the growth of many bacteria. The *p*.AB is used by the organism for the synthesis of folic and folinic acid; these mediate in the formulation processes which complete the construction of essential purines and pyrimidines from sources of carbon and nitrogen. Hitchings thought that other stages in this metabolic chain might also be vulnerable to the action of antimetabolites, and he studied drugs which antagonized the growth-promoting action of folic acid in bacterial cultures. Diaminopyrimidines were very effective antagonists (Hitchings *et al.*, 1948). Their activity could be more easily overcome by addition of folinic than by folic acid, so it is likely that this type of drug interferes in the process of conversion of folic to folinic acid.

Similar activity was noted with the antimalarial drug proguanil; the diaminopyrimidines were therefore tried against laboratory infections of malaria in chicks, canaries, mice and monkeys. From a large series of derivatives, the most active and least toxic compound, pyrimethamine, was selected (Falco *et al.*, 1951).

This drug is now widely used as a malaria suppressant. Because of its selective mode of action, it operates at the point in the life-history of the parasite when folinic acid is most in demand—during division of the nucleus. It has no great activity upon the growing parasite in the red cell, but, when the schizont is grown, the drug comes into action and prevents the formation of merozoites. Its antimalarial action is therefore slow, and is different in character from that of quinine, mepacrine, or the 4-aminoquinoline drugs, which affect parasites at all stages of development. The toxicity of pyrimethamine to the host is low, because human cells make use of pre-formed folic and folinic acid absorbed from the gut. Toxicity to the malaria parasite is high because this organism cannot utilize pre-formed folinic acid; it relies upon intracellular synthesis from *p*.AB. It is therefore more vulnerable than the host to the action of the antimetabolites.

Sulphonamides have quite powerful antimalarial activity, because they compete with *p*.AB. The metabolic chain from *p*.AB to folinic acid can therefore be interfered with at two points. If sulphonamide and pyrimethamine are given together to an animal infected with malaria, the effect is much greater than with either drug alone. The substances potentiate each other, because they block different parts of the same metabolic pathway.

Fig. 1 shows this potentiation in *Plasmodium gallinaceum* malaria in chicks (Rollo, 1955). At the most favourable combination of the two drugs, only 1/8th of the dose of pyrimethamine together with 1/7th of the dose of sulphadiazine are required to produce the effect given by either drug alone. Fig. 2 shows the effect of giving pyrimethamine and proguanil together. Both of these drugs act upon the folic-folinic acid system, and their effects are almost additive—the drugs certainly do not potentiate each other. Similarly, no potentiation is shown when pyrimethamine is given with chloroquine, a drug which has activity on a number of enzyme systems unrelated to the *p*.AB-folic acid series.

Although the potentiating action of sulphonamide and pyrimethamine has been known for some years, it has not yet been used in the treatment of human malaria. It would be of interest to know what the action of the combination of drugs would be upon strains of the parasite which show resistance to proguanil and pyrimethamine.

The potentiating effect of sulphonamides and pyrimethamine is also shown by other organisms which utilize the *p*.AB-folic acid metabolic chain. Eyles and Coleman (1952, 1953) working with experimental *Toxoplasma* infections in mice, found that this organism was resistant to all chemotherapeutic substances, except the sulphonamides, sulphones, diaminopyrimidines and aureomycin. The sulphones and aureomycin were of low activity,

and the sulphonamides were little better. The most effective of a series of diaminopyrimidines was pyrimethamine, and potentiation was observed when pyrimethamine and sulphonamides were given together. The proportions of drug in the most effective combination were 1/25 of the dose of pyrimethamine and 1/8 of the dose of sulphadiazine which would show the same degree of activity as each given alone.

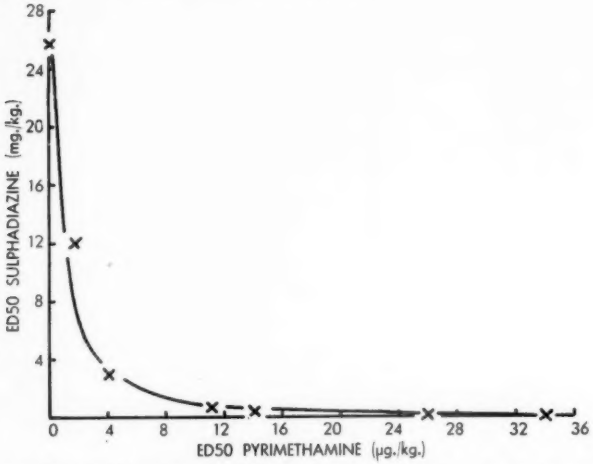


FIG. 1.—Potentiating effect of pyrimethamine and sulphadiazine in chicks infected with *Plasmodium gallinaceum* (Rollo, 1955).

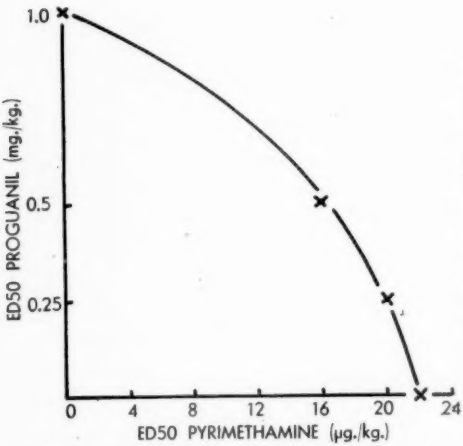


FIG. 2.—The effect of pyrimethamine and proguanil on *P. gallinaceum* in chicks (Rollo, 1955). No potentiation.

[Figs. 1 and 2 are reproduced from the *British Journal of Pharmacology*, by kind permission.]

Ryan *et al.* (1954) gave pyrimethamine and sulphadiazine to 29 patients with acquired or congenital toxoplasmic chorioretinitis, carefully checked by tests of skin sensitivity to toxoplasmin and the presence of antibodies revealed by the dye test. Many had previously been treated by other methods without success. Satisfactory clinical evidence of improvement was observed in 25 patients and 17 of them showed significant clearing of vitreous opacities. The dose of pyrimethamine used was very large—75 to 100 mg. daily, with 0·5–1·5 grams of sulphadiazine for ten days. Such doses caused nausea and had an effect upon hæmopoiesis, and although rapid recovery followed cessation of treatment or reduction of the dose, this effect of pyrimethamine must be considered when large doses are given. Supplements of folic or, better, folinic acid would be expected to reduce the toxicity of the drug to the host, without affecting its action on the parasite.

Petrovicky (1955) in Czechoslovakia also reports encouraging results upon 16 patients with positive tests for toxoplasma infection. Most of these had involvement of the nervous system, and sulphonamides and Aureomycin had failed to produce lasting improvement. Treated with pyrimethamine, 15 patients improved sufficiently to be able to return to work, although only one of the patients was given sulphonamides together with the pyrimethamine.

Smith and Perkins (1956) in London have also used pyrimethamine alone in the treatment of

toxoplasmic uveitis. As would be expected, the results, though encouraging, were not so striking as those obtained by workers who have used pyrimethamine with sulphonamides.

Fig. 3 is a diagram of the metabolic pathway to the nucleoproteins. We have considered

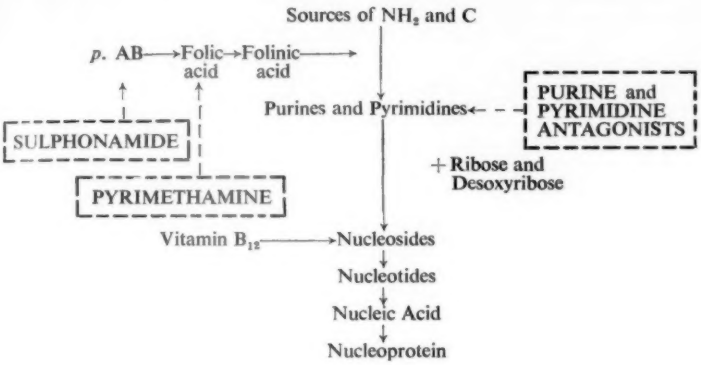


FIG. 3.

the potentiation of sulphonamides and pyrimethamine on the *p*.AB-folinic acid system; they provide a useful selectively toxic combination against organisms which use this metabolic chain. In addition, the purine and pyrimidine antagonists, such as azaserine, azaguanine, bromouracil, and mercaptopurine, interfere with the utilization of purines and pyrimidines in the manufacture of nucleosides. Sulphonamides, pyrimethamine and these compounds show a series of progressive potentiations against susceptible strains of bacteria (Elion *et al.*, 1954; Hitchings, 1955). The purine and pyrimidine antagonists are active in neoplastic diseases, because they affect those cells which are most actively synthesizing nucleoprotein. They have no significant antimalarial action, and so far as I am aware, have not been tried in toxoplasmosis.

Vitamin B_{12} also plays a part in nucleoprotein synthesis (Arnstein, 1955). Antagonists of vitamin B_{12} have been described by Lester Smith *et al.* (1956) and Cuthbertson *et al.* (1956) and may provide further stumbling-blocks to place in this metabolic pathway. There must be many possible sites of interference and drug potentiation, and our ignorance of them will be dispelled as the detailed picture of the chemistry of intermediate metabolism becomes clear (*Brit. med. J.*, 1956).

REFERENCES

ARNSTEIN, H. R. V. (1955) Biochemical Society Symposia No. 13. The Biochemistry of Vitamin B_{12}. Cambridge; p. 92.
Brit. med. J., (1956) Editorial, i, 846.
CUTHBERTSON, W. F. J., GREGORY, J., O'SULLIVAN, P., and PEGLER, H. F. (1956) *Biochem. J.*, **62**, 15P.
ELION, G. B., SINGER, S., and HITCHINGS, G. H. (1954) *J. biol. Chem.*, **208**, 477.
EYLES, D. E., and COLEMAN, N. (1952) *Publ. Hlth. Rep. Wash.*, **67**, 249.
——, —— (1953) *Antibiot. Chemother.*, **3**, 483.
FALCO, E. A., GOODWIN, L. G., HITCHINGS, G. H., ROLLO, I. M., and RUSSELL, P. B. (1951) *Brit. J. Pharmacol.*, **6**, 185.
HITCHINGS, G. H. (1955) *Amer. J. clin. Nutr.*, **3**, 321.
——, ELION, G. B., VAN DER WERFF, H., and FALCO, E. A. (1948) *J. biol. Chem.*, **174**, 765.
LESTER SMITH, E., PARKER, L. F. J., and GANT, D. E. (1956) *Biochem. J.*, **62**, 14 P.
PETROVICKY, O. (1955) *Čas. Lék. čes.*, **94**, 486, 937.
ROLLO, I. M. (1955) *Brit. J. Pharmacol.*, **10**, 208.
RYAN, R. W., HART, W. M., CULLIGAN, J. J., GUNKEL, R. D., JACOBS, L., and COOK, M. K. (1954) *Trans. Amer. Acad. Ophthal. Oto-laryng.*, **58**, 867.
SMITH, C., and PERKINS, E. S. (1956) *Proc. R. Soc. Med.*, **49**, 24.

Professor G. A. H. Buttle:

Synergy in Chemotherapy

The term "synergy" in chemotherapy is used to imply that the effect of two or more agents acting together is greater than the sum of their effects when acting separately. Synergy in chemotherapy is therefore used in the same sense as potentiation in general pharmacology and any combined effect which is less than this is termed an additive effect.

In general pharmacology potentiation between two drugs is most obvious when an enzyme which normally destroys one drug is inactivated by the potentiating drug as in the case of acetylcholine and the anticholinesterases. In chemotherapy we have, as yet, no knowledge of this type of action.

Most of the work on synergy has, so far, been purely empirical and has arisen from an examination of the behaviour of bacteria when exposed to antibiotics, while much useful knowledge has come from direct observations on patients themselves. While there are certain general rules for the combination of antibiotics, many of which rules have been elaborated by Jawetz and his colleagues, the only sure way to determine whether two agents are synergic in action is to try the effect of the combination on the rate of growth of the organism or on its complete destruction. As yet, biochemistry has contributed little of real significance but it seems possible that soon it will make a great contribution to practical chemotherapy. Thus synergy is to be expected if two or more agents were to block one pathway in the metabolism of an organism at successive points, for the result might be expected to be the product rather than the sum of the effects of the individual agents. This sequential blocking of the folic acid and folinic acid pathway is exemplified by the combined effect of pyrimethamine (Daraprim) and of sulphonamide on the malaria parasite and on coccidia respectively. The practical applications of this work may extend to a wide field of chemotherapy.

There may be another type of synergy in respect of those organisms which can develop a considerable resistance to a given antibiotic through their facility for adapting themselves to its action, particularly when prolonged treatment is necessary. In this type of synergy the two agents may be acting on different biochemical pathways; with a very potent substance like penicillin or streptomycin another will usually only be synergic if there is a tendency on the part of the organism to acquire resistance to the antibiotic. This resistance is probably due to the development of an alternative metabolic pathway or even to the organism adapting itself to the utilization of the antibiotic in place of its normal metabolite. There are many examples in bacterial chemotherapy. This type of synergic action is well known in its practical therapeutic applications as in the treatment of subacute infective endocarditis and of tuberculosis, but the biochemical implications are not yet understood.

In considering the problem of synergy in the treatment of malignant disease we have the possibility of a synergic effect in controlling the condition by the removal of one or more hormones which may help in delaying the growth of certain tumours. There is also great interest in any possible analogy between synergy as found in the treatment of infective disease and any possible synergy in the use of antimetabolite or antimytotic drugs for the treatment of malignant disease. This problem is vastly more difficult; for in infective disease we are attacking an actively multiplying invader which is in many respects different from the host cells, whereas in malignant disease we are attempting to differentiate between the malignant cell and other rapidly dividing cells of the body such as those of the bone-marrow or of the lining of the intestines. These cells in their normal activities are probably multiplying almost as rapidly as the malignant cells, and unless there are differences in their biochemistry, such as in the configuration or constitution of the nucleic acids, it is difficult to see how any chemotherapy can be effective without equivalent danger to the host. Nevertheless, there is some slight analogy with tuberculosis in that marked resistance is developed to nitrogen mustard, both in experimental tumours and in Hodgkin's disease.

In chemotherapy we have, as yet, little information of how the various agents produce their therapeutic effects but we are gaining some knowledge as to which will work best in combination with one another, and as the number of drugs increases we may find further opportunities for their combined application.

Dr. S. Brian Kendall, Veterinary Laboratory, Ministry of Agriculture, Weybridge:
Synergy between Pyrimethamine and Sulphonamides Used in the Control of Eimeria tenella

(1) *The life-history of* Eimeria tenella.—In addition to being an important pathogen of domestic fowls, *Eimeria tenella* is an unusually suitable subject for experimental investigation. The life-history follows a precise time-schedule, different developmental stages of the parasite appearing at predictable intervals and the clinical picture being characterized by sudden and violent hæmorrhage from the cæcum.

During the first 72 hours following the time of infection, the First Generation Schizonts develop superficially in the epithelium of the cæca, where they cause no evident damage. Between the 72nd and the 96th hour the Second Generation Schizonts develop more deeply in the submucosa and cause extensive tissue damage.

Between the 96th and 120th hours, rupture of the Second Generation Schizonts induces hæmorrhage which is evinced by blood-stained fæces on the fifth and sixth days following

infection. Following all but the lightest infection, a high rate of mortality can confidently be expected.

(2) *The present use of coccidiostatic drugs.*—During the past ten years several comparatively effective coccidiostatic drugs have been investigated. These include some of the sulphonamides of which sulphadimidine and sulphaquinoxaline have proved the most effective.

All drugs so far investigated, including the sulphonamides, appear to evince therapeutic activity through an inhibitory effect on the Second Generation Schizont, the growth of which is the only phase of the life-history known to be pathogenic to the chick.

At relatively low concentrations of drugs there is little apparent effect on stages which precede the Second Generation Schizont. At relatively high concentrations, however, stages other than the Second Generation Schizont may be affected.

It is important for satisfactory therapeutic control of disease not to exceed the minimum concentration of the drug which will suppress the Second Generation Schizonts.

(3) *The efficacy of coccidiostatic drugs.*—Although several of these drugs, in particular the sulphonamides, are proving effective for the control of cæcal coccidiosis under practical conditions on the farm, their use can be criticized on the grounds that the concentrations necessary to control acute disease must be so high that some degree of inappetence is liable to be caused. In some circumstances, more definite evidence of toxicity is observed. In particular, the use of sulphaquinoxaline both in the field and in the laboratory has been associated with toxicity even at concentrations below those necessary to ensure full therapeutic control.

(4) *The possibility of using drugs in synergic combinations.*—The original observation of Lux (1954) that one of a group of 2, 4-diamino-pyrimidines, i.e. 2, 4-diamino, 5, p. chlorophenyl, 6-ethyl pyrimide—pyrimethamine (Daraprim), had a synergic effect on *E. tenella* when used in combination with certain sulphonamides, was, therefore, of outstanding interest.

At Weybridge we have confirmed and extended this observation of Lux with a view to developing effective systems of chemotherapy for the control of *E. tenella* in the field. Joyner and Kendall (1955); Kendall and Joyner (1956).

(5) *Efficacy of pyrimethamine and sulphadimidine in combination.*—Fig. 1 demonstrates the effect of sulphadimidine and pyrimethamine, separately and together, on the rate of mortality in groups of chicks experimentally infected with *Eimeria tenella.* In each instance the drugs were given mixed with the food, treatment commencing on the morning of the second day following the day of infection and continuing until the morning of the fifth day.

It will be seen that a rate of mortality of 90% was observed among chicks of the untreated (Control) Group (H). Sulphadimidine at a concentration in the food of 0·05% (Group C) had no effect on the rate of mortality. At a concentration of 0·1% of the food (Group D) there was a moderate effect (a reduction in the rate of mortality from 90% to 71%). Pyrimethamine, at concentrations of 0·005% (Group A) or 0·01% (Group B) was rather

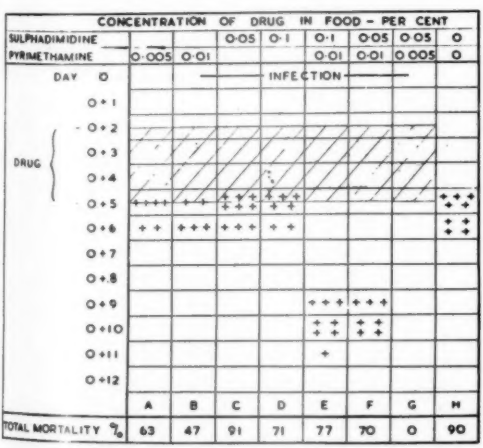


FIG. 1.—The efficacy of pyrimethamine and sulphadimidine in combination for the control of *Eimeria tenella.*

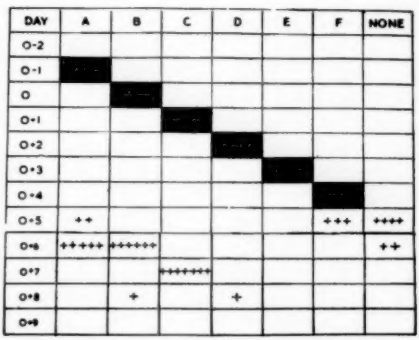


FIG. 2.—Effect of 0·4% sulphadimidine with 0·02% pyrimethamine on *Eimeria tenella.*

more effective. Even at 0·01%, however, the reduction in the rate of mortality was only about 50%.

When, however, the two drugs were given together at the lower concentrations, i.e. 0·05% sulphadimidine and 0·005% pyrimethamine, there was complete control of the disease (Column G) and there was no mortality whatsoever.

(6) *Further consideration of Fig.* 1.—In the first place it seems that the results recorded in columns E and F are anomalous in that the rates of mortality observed when sulphadimidine and pyrimethamine are used at concentrations of (0·1% with 0·01%) or (0·05% with 0·01%), are higher than with the lower concentrations used with Group G. It will be observed, however, that mortality with Groups E and F occurred on the ninth and tenth days following the day of infection (i.e. the fourth and fifth days following the termination of treatment), thus indicating a delay in the time of mortality of about four days as compared with that observed with the untreated disease.

This failure to control mortality, while delaying its onset by several days, has already been shown (Kendall and McCullough, 1952) to follow the use of sulphonamides given alone, i.e. without the synergic assistance of pyrimethamine, but at concentrations considerably higher than those ordinarily found necessary to inhibit the development of the Second Generation Schizonts.

It can be shown that excessive concentrations of the drugs cause marked but only temporary inhibition of the earlier developmental stages of the parasite and that the termination of a period of treatment is then followed by a resumption of development with hæmorrhage and death.

(7) *The effect on different developmental stages of the parasite of high concentrations of sulphadimidine and pyrimethamine.*—The different effects of the drugs on the different developmental stages of the parasite are well illustrated in Fig. 2 which shows the effects of high concentrations (0·4% sulphadimidine and 0·02% pyrimethamine) of the two drugs given together over periods of twenty-four hours on successive days following the time of infection, during the day of infection or for the day preceding infection.

It will be observed that, as usual, the mortality in the group of untreated birds occurred principally on the fifth day following the day of infection. A period of twenty-four hours' treatment, covering the second, third or fourth days following the day of infection had a marked therapeutic effect. Control of the disease was practically complete in Groups D and E and was partially effective (Group F) when treatment was delayed until the morning of the fourth day.

By contrast, treatment covering the day of infection, or the day following the day of infection, produced only temporary inhibition in the development of the parasite with no

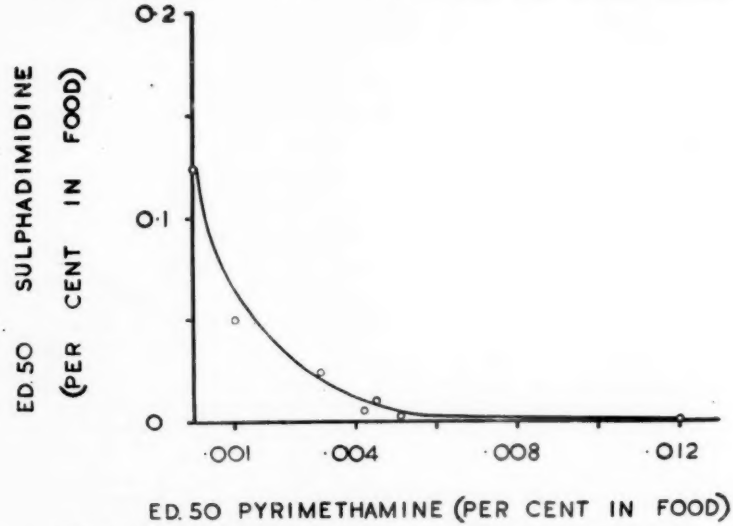


FIG. 3.—Showing the 50% protection points of different concentrations of pyrimethamine and sulphadimidine.

effect on the rate of mortality but a marked effect on the time at which it occurred. Treatment which preceded the day of infection had some effect on the time at which mortality occurred, presumably as a result of the retention in the tissues of some of the drug.

(8) *The effect of the drugs in combination is not a simple* additive *effect.*—It might be deduced from the experimental data in Fig. 1 that the combined effect of pyrimethamine and sulphadimidine was the result of *potentiation* rather than a simple *additive* effect—for it is shown that whereas neither 0·01% pyrimethamine nor 0·1% sulphadimidine has a very marked effect, half the quantities of each of the drugs in combination produce full therapeutic control.

This conclusion is confirmed by Fig. 3 which represents the relative proportions of pyrimethamine and sulphadimidine which together produce a 50% reduction in the rate of mortality.

If the effect were simply additive, then plotting the 50% inhibition doses should result in a straight line joining the point indicating inhibition with pure pyrimethamine with that indicating inhibition with pure sulphadimidine. It is shown, however, that 50% inhibition can be obtained using minimum amounts of the two drugs in combination which are less than a quarter of those required when using the drugs by themselves. The shape of the curve is very similar to that figured by Rollo (1955) when demonstrating the potentiation of sulphadiazine by pyrimethamine in the control of *Plasmodium gallinaceum*. This in itself suggests the possibility of a close analogy between the metabolism of *E. tenella* and those species of *Plasmodium* on which pyrimethamine and some sulphonamides exert a marked synergic effect.

Our work at Weybridge has, so far, supported the hypothesis that pyrimethamine and sulphadimidine act sequentially in a metabolic chain involving para-amino benzoic acid and folic or folinic acid.

The precise mechanisms involved are under investigation—by my colleague Dr. L. P. Joyner who has been, throughout, associated with this work.

ACKNOWLEDGMENTS

Thanks are due to the editors of the *Journal of Comparative Pathology and Therapeutics* (Kendall and Joyner, 1956b) for the loan of the block from which Fig. 3 has been printed and for permission to incorporate in Fig. 1 some material already in the Press.

REFERENCES

JOYNER, L. P., and KENDALL, S. B. (1955) *Nature Lond.*, **176,** 975.
KENDALL, S. B., and JOYNER, L. P. (1956a) *Vet. Rec.*, **68,** 119.
——, —— (1956b) *J. Comp. Path.*, **66,** 145.
——, and MCCULLOUGH, F. S. (1952) *J. Comp. Path.*, **62,** 116.
LUX, R. E. (1954) *Antibiotics and Chemother.*, **4,** 971.
ROLLO, I. M. (1955) *Brit. J. Pharmacol.*, **10,** 208.

Professor E. Boyland, Professor of Biochemistry, Chester Beatty Research Institute, Institute of Cancer Research, Royal Cancer Hospital:

Synergism in Cancer Therapy

In the treatment of cancer the main methods of treatment, surgery, radiotherapy and chemotherapy should be kept in mind. In the past these methods have most frequently been employed independently or sequentially, but the use of combined treatments is increasing. Chemotherapeutic agents as means of treating cancer can be grouped in four categories—hormones, antimetabolites, antibiotics and nitrogen mustard derivatives which are alkylating agents.

In hormone therapy one might include the removal of glands as "negative hormone therapy" or "negative chemotherapy" in which the sources of a hormone upon which the growth of tumours depends, are removed. Effective forms of negative hormonal chemotherapy include orchidectomy, oophorectomy, adrenalectomy and hypophysectomy—used in the control of cancer of the prostate and cancer of the breast. These operations are not usually carried out simultaneously. Thus, in some cases of breast cancer when oophorectomy has become ineffective, adrenalectomy frequently produces successful remissions. If the growth then recurs, hypophysectomy or pituitary ablation by introducing radioactive gold under radiographic control as developed by Mr. W. P. Greening and Dr. J. J. Stevenson may be performed with success. Now these operations are usually performed in sequence rather than simultaneously and each operation may give a term of useful life. As these forms of surgical treatment are not to be undertaken lightly it is probable that they should not be carried out simultaneously except perhaps for oophorectomy and

adrenalectomy. If, however, the operations of adrenalectomy and pituitary ablation and the after-care of patients could be simplified then they might be performed within a short time of each other with advantage.

The rationale of the operations of castration, adrenalectomy and hypophysectomy in cancer treatment is founded upon the fact that the growth of tumours is dependent on the presence of circulating hormones. If a tumour is dependent on the presence of sex hormones, then castration may restrict the growth by removing the sources of such hormones. In the absence of the gonads, however, the adrenals may elaborate sex hormones and so permit tumour growths. It was for this reason that Dr. Charles Huggins introduced adrenalectomy. Now if castration and adrenalectomy are performed together the hormones' deprivation might be more complete, so that the host defence mechanisms would have a better chance of destroying the neoplasm. There is also the possibility that some cancers require adrenal hormones for growth.

There are indications that cancers are either genetically unstable or readily adaptable so that in the absence of sex hormones they may become independent of such hormones. When this happens the beneficial effect of the original operation is lost. The development of this independence might be delayed if the operations were performed at the same time because the independence may be acquired by mutation of the cancer cells. If the independence to each of two hormones is controlled by separate genes then the chance of a cancer cell arising which is independent of both hormones is very much less than if only one hormone were involved.

Some tumours may be unable to grow in the absence of hormones other than the sex hormones such as prolactin (mammatrophin), growth hormone or one of the other hormones produced by the hypophysis. It is also possible that the growth of tumours dependent on hormones elaborated by the adrenals may be controlled by removal of ACTH which might, in turn, control adrenal function. There is thus the possibility that some cancers of the breast and of the prostate may be dependent both on steroid hormones elaborated by the gonads or adrenals and on one or other of the pituitary hormones. In such cases the chance of independent cancer cells arising is probably much reduced if the gonads, adrenals and pituitary are removed at an early stage of the disease, if independence to steroid hormones or pituitary hormones develop independently. If tumour cells become independent of steroid hormones then they will grow if the necessary pituitary hormone is present. If neither the steroid nor pituitary hormones are present then the possibility of hormone independent cancer cells arising is much reduced.

Chemotherapy is widely used in the handling of leukæmias and lymphadenopathy and, for these, synergic treatment should have advantages. Many cases of acute leukæmia benefit from treatment with 6-mercapto-purine (an anti-purine drug), with amethopterin (an antifolic compound) and with ACTH or cortisone. Eventually, resistance develops to all these drugs and by analogy with the results obtained in chemotherapy of infectious diseases one might expect better results if combined treatment were used. Two of these forms of treatment—amethopterin and ACTH or cortisone—are so toxic that they cannot be used continuously for very long. In this form of therapy of acute leukæmia combined treatment, which should reduce the incidence of drug resistance, must wait until other drugs which are more effective and as non-toxic as 6-mercapto-purine are available. Until that time it is probably advisable to keep the anti-folic acid compounds and cortisone or ACTH for use in the terminal stages of the disease, although successful results have been obtained with combined use of 6-mercapto-purine and cortisone.

The situation in treatment of the chronic leukæmia is similar to that with acute leukæmia in that too few effective drugs are available. Myleran and urethane produce beneficial results in myeloid leukæmia but urethane cannot be tolerated for long periods. Myleran is an extremely effective drug but patients become resistant and treatments with Myleran in combination with 6-mercapto-purine or with sodium arsenite should be worth consideration.

Many patients suffering from lymphocytic leukæmia and from Hodgkin's disease are improved by medication with the aromatic nitrogen mustards, R 1048 (2-(*bis*-2-chloroethyl) naphthylamine) or better R 1348 (4-(*bis*-2-chloroethyl) aminophenylbutyric acid). Both these compounds like the aliphatic nitrogen mustards are alkylating agents and so, presumably, act by similar mechanisms so that there would seem to be no advantage in using them together. Combined treatment of lymphadenopathies with CB 1348 and radiotherapy is sometimes effective and would seem to be a rational procedure.

Synergistic treatment is urgently needed in the therapy of malignant disease. The alkylating agents, Myleran and the aromatic nitrogen mustards are mutagens and the malignant cells are probably genetically unstable cells. There are therefore optimum conditions for the development of resistant forms and this frequently occurs. Advance in treatment of the leukæmias and lymphadenopathies is likely to follow the discovery of

drugs which are effective against these diseases while operating through different mechanisms than that of alkylation, so that they can be used in combination over long periods.

If the agents used are antimetabolites then the agents should block essential sequential processes of tumour metabolism, as suggested by Potter. Increasing knowledge of the metabolic processes of cancer and leukæmic cells should lead to the discovery of effective anti-metabolites which, used in conjunction with known agents, might allow the control of neoplastic growths.

Professor Robert Knox:

Drug Combinations in Treatment of Bacterial Infections

There is a natural attraction about the idea that two good drugs must be better than one, and, as Jawetz and Gunnison (1953) have pointed out, much of the talk about synergism of antibacterial drugs contains no more precise idea than that. Many workers, however, have been dissatisfied with the vagueness of the terms used and, in addition, have been puzzled by examples which suggested that combinations of drugs, far from enhancing the benefits of the single drugs, might actually be harmful. Attempts therefore have been made to define more precisely the words synergism and antagonism. Jawetz has suggested several definitions. In one of these (Jawetz and Gunnison, 1953), synergism is stated to occur when "the bactericidal rate of a drug combination is more rapid than that of twice the concentration of each single drug participating in the mixture".

Theoretically it seems to me that there can be no such thing as synergism. If two drugs A and B act on the same receptor in a susceptible cell then their combined effect can only be additive, not synergic. If they act on different receptors then their effect on a susceptible cell is different in kind, and therefore quantitative comparisons cannot strictly be made. To do so is rather like trying to express the power of a bishop and a knight in chess in either bishop or knight equivalents.

Apparent synergism can be caused in many ways. In some cases a so-called synergic effect can be quite simply explained on a chemical or physical basis, or by a combination of physical and chemical agents. I should like to discuss a few examples. Amygdalin and emulsin are each separately non-toxic to rabbits, but together kill, because free hydrocyanic acid is liberated when the emulsin acts on the amygdalin. Iron and oxine (8-hydroxyquinoline) separately have little action on *Staph. aureus* but together are rapidly bactericidal and Albert *et al.* (1953) has suggested an interesting explanation of this. The amine spermine inhibits and kills tubercle bacilli but only in the presence of tissues containing the enzyme spermine oxidase (Dubos, 1951; Hirsch, 1953, 1955). Clinically, the effect of penicillin is greatly increased by the use of benemid which blocks the excretion of penicillin by the kidneys. As an example of apparent synergism between a physical and a chemical agent, we have shown (Knox and Collard, 1952) that a strain of *B. cereus* could grow well at 37° C. in concentrations of penicillin up to a hundred times greater than those which completely suppressed its growth at 42° C.—presumably because the adaptive enzyme penicillinase could be synthesized at 37° C., but not at 42° C.

It may be said that none of these are examples of synergism. If that is true, then we should have to admit that synergism ceases to exist as soon as it is explained.

In medical bacteriology we must distinguish two types of effect of drugs (1) a direct effect on all the individual members of a bacterial culture and (2) a differential effect on different members of a population whereby those individuals which are resistant to one drug are successfully dealt with by another. I think it is fair to say that a drug combination which shows the second effect may not necessarily show the first. In medical bacteriology two outstanding examples of apparent "synergism" are in the combined action of antituberculous drugs such as isoniazid (I.N.H.), streptomycin and PAS and in the combined effect of streptomycin and penicillin on certain types of streptococci. It is not at all easy to distinguish the two types of effect, but it would seem that the effect of combined chemotherapy in tuberculosis is to be explained partly at least as due to a delay in the development of resistance though certain drug combinations are much more bactericidal than single drugs. Even here it is not always easy to be certain that the two drugs are not killing different members of the population. As regards certain streptococci, it seems clear that penicillin and streptomycin have a greatly increased bactericidal action out of all proportion to the effect of the single drugs. Klein and Schorr (1953) showed that synergism was most marked with combinations of drugs to which resistance developed most rapidly when they were used singly. Clinically, antituberculous drug combinations are most effective in precisely those types of tuberculosis in which development of clinical resistance is most marked when the drugs are used singly, for example, in chronic pulmonary tuberculosis.

It must be admitted that our present techniques for measuring synergism *in vitro* are unsatisfactory. Garrod (1953) has indicated the possible value of a simple test for the bactericidal efficiency of drug combinations and Stern and Elek (1955) have attempted to measure bactericidal effects of drug combinations by the use of Lederberg's ingenious replica plating technique. As regards the resistance delaying type of effect, it is possible by *in vitro* tests to show that resistance of *M. tuberculosis* to certain drugs can be delayed by drug combinations. We are at present investigating the value of semi-solid agar media for this purpose (Knox, 1955).

There is, however, little doubt that we shall not get far along purely empirical lines. Pittillo and Foster (1954) have recently made an interesting approach and have shown that synergism could be predicted in pairs of drugs whose action was known to be reversed by the same metabolite.

One of the great difficulties is to distinguish between multiple effects on single bacterial cells and effects on different cells in a bacterial population. The study by De Lamater, Maaloe and others of morphological changes produced by anti-bacterial drugs is an attempt to investigate such effects at the cellular level by using the techniques of microscopic cytology (Spooner and Stocker, 1956). In our own laboratory we have tried to eliminate difficulties caused by selection by investigating the effect of drug combinations on the respiration of washed suspensions of *M. tuberculosis* by Warburg's manometric technique (Meadow and Knox, 1956). Here we found some evidence that for example, streptomycin and isoniazid in concentrations which separately did not inhibit respiration showed a more than additive effect when combined.

Albert (1951) says in his admirable book on Selective Toxicity "It follows from the various facts which we have just been reviewing that comparative biochemistry is, of all branches of science, the one that holds the master key for the logical discovery of selectively toxic agents."

REFERENCES

ALBERT, A. (1951) Selective Toxicity. Methuen's Monographs on Biochemical Subjects. London.
——, GIBSON, M. I., and RUBBO, S. D. (1953) *Brit. J. exp. Path.*, **34,** 119.
DUBOS, R. J. (1951) *Amer. Rev. Tuberc.*, **63,** 119.
GARROD, L. P. (1953) *Brit. med. J.*, i, 953.
HIRSCH, J. G. (1953) *J. exp. Med.*, **97,** 327.
—— (1955) Ciba Foundation Symposium on Experimental Tuberculosis, p. 115.
JAWETZ, E., and GUNNISON, J. B. (1953) *Pharmacol. Rev.*, **5,** 175.
KLEIN, M., and SCHORR, S. E. (1953) *J. Bact.*, **65,** 454.
KNOX, R., and COLLARD, P. J. (1952) *J. gen. Microbiol.*, **6,** 369.
——, (1955) *Lancet*, ii, 110.
MEADOW, P., and KNOX, R. (1956) *J. gen. Microbiol.*, **14,** 414.
PITTILLO, R. F., and FOSTER, J. W. (1954) *J. Bact.* **67,** 53.
SPOONER, E. T. C., and STOCKER, B. A. D. (1956) 6th Symp. Soc. Gen. Microbiol, London.
STERN, H., and ELEK, S. D. (1955) *Brit. med. J.*, ii, 1304.

Dr. H. O. J. Collier: May I ventilate further the question of the semantics of "synergy", or "synergism", as usage has it? It is quite true, as Professor Buttle said, that what pharmacologists would call "potentiation", chemotherapists have called "synergism". For example, Eagle and Fleischman (1948) applied the latter term to the potentiation of penicillin by bacitracin in rabbit syphilis, and I plead guilty to having used the term "synergism" myself in describing the potentiation of sulphonamides by diaminopteridines (Collier, Hall and Waterhouse, 1950). However, I feel it would be better if in chemotherapy the word "potentiation" were always used for a degree of synergism which is greater than additive, while "synergism" or "synergy" were used as a broad term, covering all forms of "working together" from potentiation to merely partial addition.

The most convenient way in which these terms may be defined is provided by the diagram of Gaddum (1953). In this diagram, which applies to the relation of two substances, the amount of each, either alone or mixed, required to produce a given biological effect (such as 50% lethal, curative or effective dose) are plotted. The existence potentiation, addition or antagonism is readily seen from the course of the resulting curve.

REFERENCES

COLLIER, H. O. J., HALL, I. F. and WATERHOUSE, P. D. (1950) *Amer. J. trop. Med.*, **44,** 161.
EAGLE, H. and FLEISCHMAN, R. (1948) *Proc. Soc. exp. Biol., N.Y.*, **68,** 415.
GADDUM, J. H. (1953) Pharmacology. 4th Edn. London. p. 480.

Professor A. Albert: In his wisdom, Professor Buttle lost no time in directing our thoughts to what is called "sequential blocking". There can be little doubt that this is one of the most effective mechanisms of synergy. Current biochemical studies make us visualize a growth factor (e.g. folinic acid) being gradually built up from components as it moves along a "production line", each stage of assembly being carried out by a different enzyme. What, then, is the arithmetic of sequential blocking? If we block the first enzyme to the extent of 90%, then only 10% of the partly completed factor reaches the second enzyme. If we are lucky enough to have discovered how to block the second enzyme also by 90%, then only 1% of the (still incomplete) factor emerges, and that is little enough.

But, it may be asked, why not simply use more of the first drug, and block the first enzyme by 100%? The answer is that the patient would probably die first. Pharmacologists are familiar with the exponential effect of drugs on tissues: a large increase in the drug concentration causes little extra response. This is, after all, only a special application of the familiar principle of adsorption from solution, which follows a hyperbolic curve: the Langmuir isotherm (Langmuir, 1916). A simple and familiar example of this behaviour is the adsorption of acetic acid from water, in which it has been dissolved, on to grains of carbon suspended in the water. If it is desired to make twice as much acetic acid become adsorbed on the carbon, the solution may have to be made ten times stronger in acetic acid. Thus to increase enzyme blocking from 90 to 100% would usually call for a quite inordinate amount of the drug and so endanger the patient's life.

The other effective mechanism of synergy is to use a substance, preferably something that is pharmacologically inert, to prevent the drug from being wasted at what Veldstra (1948) calls "sites of loss".

When a drug is introduced into the body it usually has to penetrate several semi-permeable membranes before it reaches its target, the "receptor". For example, mepacrine given orally in malaria, has to penetrate the gut-blood barrier, the red-cell membrane, and possibly that of the parasite. At every stage the active drug is involved in an equilibrium with the following processes: (*a*) Storage, (*b*) Elimination, (*c*) Destruction, (*d*) Diffusion towards the receptor.

Concerning storage, this may be good (e.g. when it helps to maintain a constant blood-level in malaria), or bad (e.g. when a drug is given as a hypnotic to a bread-winner). In the latter case, storage is waste, and so are elimination (e.g. by the kidneys) and destruction.

Waste by storage often occurs in fat (liposoluble drugs) and in tissues rich in nucleic acid (cationic drugs). Working with plant growth-substances, Veldstra (1948) showed that simple analogues, having no growth-promoting action, could intensify tenfold the action of such substances as naphthylacetic acid, and that the analogues did this by saturating "sites of loss", which were lipoid in nature. He also explained in this way the remarkable activating effect of sesamin on pyrethrin in fly-sprays, a synergy born of the acute scarcity of pyrethrin during the Second World War.

Waste by excretion is controllable in the case of penicillin by the administration of benemid or caronamid, which block the particular elimination process in the kidneys.

Waste by destruction may soon be brought under control, following upon the brilliant experiments of Brodie and his colleagues in the National Heart Institute, Bethesda (Brodie, 1955). These workers showed that a simple aromatic ester (SKF 525) potentiates such diverse drugs as hypnotics, analeptics and analgesics by inhibiting a set of enzymes (of the triphosphopyridine-nucleotide class) which exist in the microsomes of liver apparently to dispose of foreign chemicals (including amines derived from putrefaction in the bowels). These enzymes are capable of carrying out at least five different types of destructive chemical reaction. This otherwise inert substance, SKF 525, blocks these destructive enzymes, and allows the patient to have a much higher proportion of the administered dose than otherwise.

REFERENCES

BRODIE, B. B. (1955) *Science*, **121**, 603.
LANGMUIR, I. (1916) *J. Amer. Chem. Soc.*, **38**, 2221; (1917) **39**, 1848.
VELDSTRA, H. (1948) *Bull. Soc. Chim. biol., Paris*, **30**, 772; (1956) *Pharmacol. Rev.*, in the press.

Professor L. P. Garrod: I agree with previous speakers that the choice and definition of terms in connection with this subject is difficult: what I have heard in discussion has almost persuaded me that the word "potentiation" should replace "synergy" in describing some effects seen in chemotherapy. Although it may be questionable whether some effects qualify for this description, there can be no doubt when a combination of drugs achieves something which neither drug alone will produce in any dose. An example of this is the action of penicillin with streptomycin on *Streptococcus fæcalis* (E. Jawetz (1952) *Arch.*

intern. Med., **90**, 301). The action of penicillin on this organism exhibits the zone phenomenon, the optimum concentration being 6 μg. per ml. This produces only an incomplete bactericidal effect, but if streptomycin be added, even in a concentration itself without action alone, the preparation is sterilized.

An effect of this type is not often essential for successful therapy, and it is doubtful whether many tests of combined action need be carried out in a clinical laboratory. When they have to be, simple diffusion methods such as that employing antibiotics in blotting paper strips at right angles, should probably not be depended on. Replica plates from such preparations give also some information about bactericidal action, but we have preferred for some years in my laboratory to test combined action in tubes of liquid media which are plated after overnight incubation to determine whether there has been a bactericidal as well as bacteriostatic effect. To test four main antibiotics in this way (penicillin, streptomycin, chloramphenicol and a representative of the tetracyclines) singly and in every possible combination, each in a single appropriate concentration, requires only ten tubes.

Dr. J. K. A. Beverley: Sulphadimidine, 4.4′ diamino-diphenylsulphone, and pyrimethamine, are all anti-toxoplasma drugs. In the treatment of generalized toxoplasmosis in mice following intra-nasal instillation of the R.H. strain, the medium effective dose (M.E.D.) of sulphadimidine bringing about survival for twenty-eight days is 30 mg.% in the diet, while that of pyrimethamine is 5 mg.% in the diet. The most effective combination of those two drugs giving the same result, is 10 mg.% of sulphadimidine and 0·3 mg.% of pyrimethamine. There is a similar synergy between 4.4′ diamino-diphenylsulphone and pyrimethamine, but not between sulphadimidine and the sulphone, only an additive effect.

Eyles using a different strain of *Toxoplasma* and a different route of inoculation showed that there was synergy between sulphadiazine and pyrimethamine using a ten-day survival as a basis of estimating the M.E.D.

We have found that the superiority of a combination of pyrimethamine with either of the other two drugs over any of the drugs alone, was even more marked when survival for a total of fifty-six days (twenty-eight days on treatment followed by twenty-eight days on normal diet) and then demonstration of freedom from the carrier state were taken as criteria of effectiveness.

Treatment with these drugs will protect rabbits from the fatal effect of toxoplasma infection, but will not prevent local damage at the site of inoculation. When the skin is inoculated there is ultimate healing with only minor scarring, but when the anterior chamber of the eye is used, gross irreparable damage follows. This local damage can be minimized by the concurrent administration of cortisone, and there is ultimately perfect function. Cortisone, when given alone, has no effect.

Section of Endocrinology

President—A. C. CROOKE, M.A., M.D.

[*April* 25, 1956]

Primary Aldosteronism

By M. D. MILNE, M.D., M.R.C.P., and R. C. MUEHRCKE, M.D.

Department of Medicine, Postgraduate Medical School of London

ALDOSTERONE, the natural mineralo-corticoid of the adrenal cortex, has a profound influence on sodium and potassium metabolism. It reduces the sodium and increases the potassium content of many secretions and excretions, including urine, saliva, sweat, and fæces. In addition, it probably influences the distribution of sodium and potassium between the extra- and intra-cellular compartments with production of a low plasma potassium irrespective of actual potassium depletion. Quantitatively, its action on the composition of the urine is of especial importance. Aldosterone increases tubular reabsorption of both sodium and chloride, and promotes exchange of potassium from tubular cells for sodium in intra-tubular fluid. This causes retention of sodium and chloride and excess urinary loss of potassium.

Increased production of aldosterone may be divided into three main types, which in order of importance may be termed physiological, secondary, and primary aldosteronism. Physiological aldosteronism is produced by any stimulus causing sudden reduction of blood volume, e.g. excess sweating, severe hæmorrhage, surgical shock, and loss of fluid from the gastro-intestinal tract. Teleologically, this is a beneficial mechanism which reduces sodium loss and prevents any further decrease of extra-cellular fluid volume. Secondary aldosteronism occurs in clinical states associated with severe œdema, especially congestive heart failure, the nephrotic syndrome, and cirrhosis of the liver. A spontaneous or therapeutic diuresis is often associated with reduction of aldosterone production.

Primary aldosteronism was first described by Conn (1955), and 3 other cases have since been published in detail (Table I). Many other examples of this condition are known to have been diagnosed and successfully treated (Conn and Louis, 1956). 2 cases of primary aldosteronism have been treated during the last year at Hammersmith Hospital (Table I). All cases have shown an excessive urinary potassium loss with associated potassium depletion. No satisfactory explanation has been given for the predominance of sodium retention in physiological and secondary aldosteronism and of potassium depletion in the primary type. Mach *et al.* (1955) have described a somewhat unconvincing case of primary aldosteronism associated with sodium retention and unexplained generalized œdema. No attempt was made to determine whether this patient had an adrenal tumour with possibility of surgical cure.

TABLE I.—CASES OF PRIMARY ALDOSTERONISM DESCRIBED TO DATE

Case	Age and sex	Race	Duration of disease	X-ray evidence of tumour	Size and side of tumour	B.P.	Serum electrolytes mEq./l. Na	K	Cl.	HCO_3
Conn and Louis, 1954–56	34 F.	White	7 years	Not carried out	40 mm. R	175/105	148	1·8	102	37
Mader and Iseri, 1955	33 F.	Coloured	6 months	Negative	25 mm. L	170/108	143	1·6	84	42
Foye and Feichtmeir, 1955	60 M.	Coloured	8 months	Positive	40 mm. R	175/112	150	1·8	90	53
Chalmers *et al.*, 1956	43 F.	White	3 years	Positive	25 mm. R	220/150	147	1·7	104	29
Hammersmith, 1st case	43 F.	Coloured	12 years	Positive	33 mm. R	180/110	145	1·4	87	40
Hammersmith, 2nd case	58 F.	White	1 year	Negative	14 mm. L	190/105	145	2·0	97	40

Table I summarizes the clinical findings of the 6 cases of primary aldosteronism in which detailed information is available. The condition is associated with hypertension which is usually comparatively mild, and by characteristic abnormalities of plasma electrolytes. Sodium and bicarbonate levels are increased whilst potassium and chloride are reduced. All patients except the second Hammersmith case had attacks of hypokalæmic muscular weakness or paralysis, sometimes associated with paræsthesiæ and tetany. Despite gross potassium depletion most patients were surprisingly well in the intervals between attacks. Only one of the cases was a male, the condition being due to an adrenal cortical carcinoma. An adrenal cortical adenoma was found in all of the 5 female cases. There has been a surprisingly high incidence in negro patients.

The 2 patients studied at Hammersmith Hospital were widely different in severity and mode of presentation. The first case is one of the most severe examples of the disease, whilst the second is the only patient with asymptomatic primary aldosteronism yet described. *Case I* had a twelve-year history of attacks of prolonged hypokalæmic muscular paralysis which on one occasion lasted twenty-one days. In familial periodic paralysis the longest recorded duration of a single attack is eight days (Maclachlan, 1932). A clinical description of this patient, who was originally incorrectly diagnosed as "potassium-losing nephritis", has previously been published (Evans and Milne, 1954). Balance data showed she was deficient of 1,000 mEq. of potassium, equivalent to about one-third of the total normal body content. An adrenal cortical adenoma, 4 cm. in diameter, has since been removed by Professor Ian Aird (Fig. 1). This was followed by reduction of blood pressure and relief of hypertensive

FIG. 1.—Section of adrenal gland from *Case I.* Normal adrenal cortex and medulla on the left. Aldosterone-secreting adrenal cortical adenoma consisting of large lipoid-containing cells on the right. The tumour is surrounded by a fibrous capsule. ×27.

FIG. 2.—Whole le adrenal gland, *Case I* Although the total si and weight of the glan is not increased, a sma discrete aldosteron secreting tumour present.

cardiac failure. Plasma electrolytes and urinary potassium are now within normal limits. Unfortunately, this patient had histological evidence of severe bilateral chronic pyelonephritis with early irreversible renal failure. We consider this is secondary to renal damage from prolonged potassium deficiency. Irreversible renal damage was also found in the case reported by Chalmers *et al.* (1956), but in this case was mainly of hypertensive origin.

Case II.—This patient originally complained of a mild and transient occipital headache and afterwards was completely asymptomatic. Routine clinical examination showed that there was some hypertension with slight left ventricular enlargement. Electrocardiography was suggestive of potassium depletion, and this was confirmed biochemically. Balance data showed that she was in fact 400 mEq. potassium deficient. Although there was mild renal functional impairment with excess urinary potassium loss, needle biopsy of the right kidney was normal. This was considered to be highly suggestive of primary aldosteronism. Perirenal air insufflation with tomography failed to show an adrenal tumour and urinary aldosterone was reported to be normal. In view of the risk of subsequent renal and cardiac damage surgical exploration was considered to be indicated. Professor Aird successfully

removed the left adrenal gland which contained a small encapsulated adenoma (Fig. 2). This operation gave a striking demonstration of the advantages of the anterior abdominal approach since both adrenals were carefully examined before excision of the left abnormal gland. The blood pressure and biochemical abnormalities have since returned to normal and the diameter of the heart shadow has decreased. This case is the mildest example of the disease yet described, and the adenoma is the smallest aldosterone-secreting tumour recorded.

We think it probable that all cases of primary aldosteronism are at first similar to *Case II.* As potassium depletion increases, symptoms of hypokalæmic weakness or paralysis make the diagnosis more obvious. In the later stages there is grave risk of irreversible damage as found in *Case I.* Primary aldosteronism may be exceedingly difficult to distinguish from cases of so-called "potassium-losing nephritis" where hypokalæmia is directly due to primary renal disease. Since secondary irreversible renal lesions may develop in primary aldosteronism clinical differentiation may be almost impossible (Aird *et al.*, 1956). Obviously, final proof of the diagnosis rests on the demonstration of an adrenal tumour and surgical cure by unilateral adrenalectomy. Peri-renal air insufflation with tomography showed an adrenal tumour in 3 of the 5 cases in which it was used. Many cases recently described as examples of "potassium-losing nephritis" have been inadequately investigated as X-ray examination of the adrenals was not performed. Confusion may be further increased if future cases of the disease are shown to be due to adrenal cortical hyperplasia rather than to a unilateral tumour. We would not be willing to accept such a case as proven unless subtotal adrenalectomy resulted in permanent cure. It is far too early to attempt to assess the actual incidence of primary aldosteronism. The severe examples of the disease showing frank hypokalæmic paralysis must obviously be rare. It is possible, however, that milder cases similar to *Case II* may be considerably more common. Ewing (1940) found 3 adrenal cortical tumours of significant size in 1,500 consecutive necropsies. It is feasible that many such tumours previously dismissed by pathologists as of no clinical importance may, in fact, have been aldosterone-secreting tumours similar to the adenoma in *Case II.* Such cases can only be recognized by electrocardiography and biochemical investigation of cases of benign hypertension. No purely clinical method of diagnosis is available in the early stage prior to severe potassium depletion with weakness or frank periodic paralysis.

REFERENCES

AIRD, I., MILNE, M. D., and MUEHRCKE, R. C. (1956) *Brit. med. J.*, i, 1042.
CHALMERS, T. M., FITZGERALD, M. G., JAMES, A. H., and SCARBOROUGH, H. (1956) *Lancet*, i, 127.
CONN, J. W. (1955) *J. Lab. clin. Med.*, **45**, 3, 661.
—— and LOUIS, L. H. (1956) *Ann. intern. Med.*, **44**, 1.
EVANS, B. M., and MILNE, M. D. (1954) *Brit. med. J.*, ii, 1067.
EWING, J. (1940) Neoplastic Diseases. 4th Ed. Philadelphia and London.
FOYE, L. V., and FEICHTMEIR, T. V. (1955) *Amer. J. Med.*, **19**, 966.
MACH, R. S., FABRE, J., MULLER, A. F., and NEHER, R. (1955) *Schweiz. med. Wschr.*, **85**, 1229.
MACLACHLAN, T. K. (1932) *Brain*, **55**, 47.
MADER, I. J., and ISERI, L. T. (1955) *Amer. J. Med.*, **19**, 976.

The Significance of the Assay of Aldosterone in Human Urine and Blood

By O. GARROD, M.D., SYLVIA A. SIMPSON, B.Sc., and J. F. TAIT, Ph.D.

Middlesex Hospital Medical School, London, W.1

A REALIZATION of the significance of the assay of aldosterone in body fluids must depend on our present knowledge of the nature of the whole adrenocortical secretion. In this connexion it is probably necessary to consider only those hormones which have an effect in prolonging the life of adrenalectomized animals and in particular their action on mineral metabolism.

The results of Farrell and co-workers (1955) on the analysis of the adrenal venous blood of the dog are probably the most complete and quantitative which have so far been published for any mammal. In both hypophysectomized and control dogs, the major compounds secreted on a weight basis were cortisol and corticosterone; deoxycorticosterone, 17 hydroxy-deoxycorticosterone and aldosterone being produced in smaller quantities. However, taking the relative potencies of the compounds in maintaining patients with Addison's disease in electrolyte balance as an index of their effect on mineral metabolism, aldosterone would appear to be the most significant hormone secreted by the hypophysectomized dog, accounting for about 90% of the activity in the blood. Due to the operative procedure, the adrenal glands of the control dogs are actually stimulated by large amounts of endogenous

ACTH and aldosterone accounts for only about 50% of the electrolyte activity in their blood. The adrenal gland of the intact dog under normal ACTH control probably secretes cortisol and corticosterone in amounts intermediate between these two conditions and hence aldosterone would again be expected to be the dominant hormone as regards mineral metabolism. These results can probably be extrapolated to the normal human for, as far as is known, the adrenal secretion of the two species is similar.

However, as is also indicated by these results, aldosterone need not necessarily exert the major action in all circumstances. One example of this is the action of ACTH on the urinary Na/K ratio of humans (Nabarro, 1954). As Luetscher and Johnson (1954) have shown that ACTH gel does not increase the excretion of aldosterone presumably this effect must depend on the electrolyte activity of cortisol and corticosterone and perhaps other ACTH stimulated compounds. Similarly certain cases of Cushing's syndrome with electrolyte disturbances may show greatly increased cortisol and corticosterone with normal or subnormal aldosterone excretion (Ayres *et al.*, 1956*a*). Eberlain and Bongiovanni (1955) recently described a case of adrenogenital syndrome with hypertension in which, presumably as the result of the absence of 11 hydroxylase in the gland, deoxycorticosterone and 17 hydroxydeoxycorticosterone replaced corticosterone and cortisol as adrenal hormones. Prader *et al.* (1955) have described cases of salt-losing adrenogenital syndrome with normal excretion of aldosterone. In both these types of adrenogenital syndrome it is unlikely that aldosterone is the dominant adrenal hormone in controlling mineral metabolism.

Similar considerations make it dangerous to assume that the measurement of salt-retaining activity in crude extracts of body fluids can be interpreted as specific measurements of aldosterone. It is of interest, in this respect, that the only groups which have reported an increase in the excretion of aldosterone after ACTH stimulation have used analytical methods involving the bio-assay of crude extracts of urine. An even more important disadvantage of such methods is the invalidation of assays by the effects of toxic impurities on the salt excretion of adrenalectomized animals.

The main difficulty in devising an analytical method for aldosterone arises from its low rate of secretion. Analysis of animal adrenal venous blood (Farrell *et al.*, 1955; Singer and Stack-Dunne, 1955; Simpson, Tait and Bush, 1952), human peripheral blood (Simpson and Tait, 1955) and human urine (Ayres, Simpson and Tait, 1956*b*) and consideration of the amounts of the two compounds required to maintain patients with Addison's disease in normal metabolism (Hetzel, McSwiney, Mills and Prunty, 1956; Thorn, Laidlaw and Goldfien, 1955) makes it likely that the venous blood of the human adrenal gland contains aldosterone and cortisol in a ration of 1 to 60. As the specific measurement of cortisol or its metabolites still presents some difficulty, the task in the case of aldosterone seems formidable. However, reliable measurements of aldosterone in body fluids have already been made under various conditions and this has been possible because of four rather unique properties of the compound. These are:

(*a*) Its high biological potency in tests measuring the effects of hormones on the urinary electrolytes in adrenalectomized animals (Simpson and Tait, 1952).

(*b*) Its mode of conjugation in urine. This conjugate, as first discovered by Luetscher and Johnson (1954) is split by mild acid treatment, releasing the free compound. Thus, human urine treated in this way contains twenty times more aldosterone than is obtained by neutral extraction. Other steroids such as cortisol do not seem to be conjugated in this manner and hence the ratio of free cortisol/aldosterone, which can be extracted after acid treatment of human urine, is of the order of 4 : 1 only.

(*c*) Its behaviour on partition or paper chromatography. In the propylene glycol-toluene system of paper chromatography devised by Zaffaroni and Burton (1951) aldosterone runs at the same speed as cortisone. In the C system devised by Bush (1952), however, it runs at the same speed as cortisol. Thus by running the extract in the Zaffaroni system, eluting the cortisone spot and re-running the eluate in the Bush system, aldosterone can be obtained, substantially purified from cortisone, cortisol, and many other compounds. Similar methods employing partition column chromatography have been used (Simpson and Tait, 1955).

(*d*) Unlike other natural active adrenal hormones which form mono-acetates, aldosterone can produce a diacetate on acetylation in over 95% yield. After a preliminary purification of the free compound, the diacetate can easily be separated from other mono-acetates by column or paper chromatography (Simpson and Tait, 1955; Farrell *et al.*, 1955).

Of the reliable methods the most commonly used by workers is bio-assay of material purified by paper or column chromatography. Luetscher and his co-workers have recently employed a method in which the aldosterone is chromatographed in both the Bush and Zaffaroni systems before bio-assay, and the results of such a procedure should be very reliable if recoveries are carefully controlled. The only physico-chemical method published

to date (Neher and Wettstein, 1955) measures the soda fluorescence (Bush, 1952) of the compound on paper by visual examination after purification on both the Zaffaroni and Bush systems. This method has the disadvantage that any cortisol or similar compound remaining in the eluate of the cortisone spot of the Zaffaroni chromatogram will be measured as aldosterone. However, if a neutral extraction of free steroids in the urine were carried out before the measurements of the aldosterone released by acid hydrolysis, this physico-chemical method would probably be of clinical value even when the urinary content of cortisol and cortisone is high, as in many cases of Cushing's syndrome.

The method now employed in our laboratory, which is similar in principle to that of Farrell and his co-workers (1955) and has also been used for preparing crystalline aldosterone (Simpson and Tait, 1955), consists essentially of the extensive purification of the diacetate followed by an objective measurement of the soda fluorescence. Concomitantly specific measurements of cortisol can be made. Trace amounts of radioactive cortisol are added to 1 litre of a twenty-four-hour collection of urine, which is then continuously extracted with chloroform at room temperature and pH 1 for twenty-four hours. After further hand extraction and washing, the chloroform extract is purified by silica gel chromatography (Bush and Sandberg, 1953). The dried residue from the ethyl acetate:methanol fraction is chromatographed on a kieselguhr partition column (Simpson and Tait, 1955) in which aldosterone and cortisol appear reproducibly together in the same effluent fractions. An aliquot for bio-assay for comparison purposes may be taken at this stage. After acetylation and addition of 0·5 μg (^{14}C-carboxyl) aldosterone diacetate these fractions are then chromatographed on another partition column in which the mobile phase is changed after the appearance of the aldosterone diacetate in the effluent. Aliquots of the fractions are analysed for radioactivity, and those two containing most activity are paper chromatographed (Bush, 1952). The developed soda fluorescence is measured quantitatively by a fluorimeter arrangement (Ayres, Simpson and Tait, 1956*c*). The specific activity of the steroids is thus obtained, and hence the amounts initially present in the urine may be calculated. A comparison of the results obtained for the measurement of aldosterone by bio-assay and the physico-chemical method for five normal urines gave good correlation. Recoveries of free steroids throughout the procedure were about 70%. The co-efficient of variation for duplicate determinations of aldosterone was 11%.

This method, although probably of the required specificity, sensitivity and accuracy, is very laborious. It is tempting to believe that as a knowledge of the metabolites of the hormone is gained, much easier methods will be evolved. The urinary excretion of tetrahydrocortisone plus tetrahydrocortisol in normal subjects is about 6 mgm./day (Bush, 1956), the secretion of cortisol being about 20 mgm./day. For the reasons previously presented, the secretion of aldosterone is probably about 250 μg./day. The maximal amount of the metabolites of aldosterone excreted in the urine would therefore be expected to be 250 μg./day, and that of any tetrahydro compound, not more than 60 μg./day. The only known measurable metabolite of aldosterone would appear to be the presumed conjugate which, on acid hydrolysis, yields 10 μg. free aldosterone/day. According to the above quantitative speculations, this should represent an appreciable fraction of the excretion products of this hormone, and it is doubtful whether the analytical procedure could be greatly simplified as a result of the characterization of any tetrahydro derivatives of aldosterone unless a particularly specific reaction is developed.

The measurement in peripheral blood presents an even greater problem as the concentration of the free compound appears to be 0·08 μg. per 100 ml. whole blood and is not increased by acid hydrolysis (Simpson and Tait, 1956). In these circumstances, a discussion of the relative advantages of blood and urine measurements would be largely of academic interest. The assumptions involved in the extrapolation of such measurements to the assessment of the actual adrenal secretion are not unique to aldosterone and have been discussed elsewhere.

As will be described in the next paper, these methods for the assay of aldosterone have been applied to problems concerning the role of the hormone in conditions of secondary aldosteronism and the normal processes of mineral metabolism. Problems arising from their application to cases of primary aldosteronism have been discussed elsewhere (Garrod, Simpson and Tait, 1956).

We wish to thank Dr. I. E. Bush for allowing us to quote unpublished data.

REFERENCES

AXELRAD, B. J., JOHNSON, B. B., and LUETSCHER, J. A., Jr. (1954) *J. clin. Endocrin.*, **14**, 783.
AYRES, P. J., GARROD, O., SIMPSON, S. A., and TAIT, J. F. (1956*a*) Unpublished observations.
——, SIMPSON, S. A., and TAIT, J. F. (1956*b*) *J. Endocrin.*, **13**, xxxii.
——, ——, —— (1956*c*) *Biochem J.*, **62**, 8.

BUSH, I. E. (1952) *Biochem. J.*, **50**, 150.
—— (1956) Personal communication.
——, and SANDBERG, A. A. (1953) *J. biol. Chem.*, **205**, 782.
EBERLAIN, W., and BONGIOVANNI, A. (1955) *J. clin. Endocrin.*, **15**, 1531.
FARRELL, G. L., RAUSCHKOLB, E. W., and ROYCE, P. C. (1955) *Amer. J. Physiol.*, **182**, 269.
GARROD, O., SIMPSON, S. A., and TAIT, J. F. (1956) *Lancet*, i, 860.
HETZEL, B. S., MCSWINEY, R. R., MILLS, I. H., and PRUNTY, F. T. G. (1956) *J. Endocrin.*, **13**, 112.
LUETSCHER, J. A., Jr., and JOHNSON, B. B. (1954) *J. clin. Invest.*, **33**, 1441.
NABARRO, J. D. N. (1954) *Lancet*, ii, 1101.
NEHER, R., and WETTSTEIN, A. (1955) *Acta endocr., Copenhagen*, **18**, 382.
PRADER, A., SPAHR, A., and NEHER, R. (1955) *Schweiz. med. Wschr.*, **85**, 1095.
SIMPSON, S. A., and TAIT, J. F. (1952) *Endocrinology*, **50**, 150.
——, —— (1955) *Recent Progr. Hormone Res.*, **11**, 183.
——, —— (1956) Unpublished observations.
——, ——, and BUSH, I. E. (1952) *Lancet*, ii, 226.
SINGER, B., and STACK-DUNNE, M. P. (1955) *J. Endocrin.*, **12**, 130.
THORN, G. W., LAIDLAW, J. C., and GOLDFIEN, A. (1955) In: Ciba Foundation Colloquia on Endocrinology. London; **8**, 343.
ZAFFARONI, A., and BURTON, R. B. (1951) *J. biol. Chem.*, **193**, 749.

Some Factors Affecting Aldosterone Secretion

By O. GARROD, M.D., SYLVIA A. SIMPSON, B.Sc., and J. F. TAIT, Ph.D.

WE propose to review, rather briefly, some recent experimental data bearing on the control of aldosterone secretion. The first question is whether aldosterone is to any great extent under the control of ACTH, or indeed of any pituitary hormone. There is now much evidence to suggest that it is not.

First, there are the studies in hypophysectomized animals and in patients with hypopituitarism. Singer and Stack-Dunne (1955) found a much greater reduction of corticosterone than of aldosterone secretion in hypophysectomized, as compared with intact, rats, measured by the hormone output in adrenal venous blood, corticosterone being the predominant glucocorticoid in this species. Farrell and his group (1955) have reported similar findings in the hypophysectomized dog, cortisol secretion falling much more than that of aldosterone. In man, Luetscher and Axelrad (1954) have reported normal aldosterone excretion in 2 patients with severe hypopituitarism.

What effect does ACTH have on aldosterone production? When we were measuring steroids in the blood we found, two and a half hours after an injection of 25 units of ACTH, that there had been a five-fold rise in plasma cortisol, but no effect on the plasma aldosterone (Simpson and Tait, 1955). Axelrad *et al.* (1954) showed that large doses of ACTH gel did not increase the urinary aldosterone excretion and that the high outputs of this hormone usually found in the œdematous phase of the nephrotic syndrome fell to normal or subnormal levels when diuresis was induced by ACTH (Luetscher and Curtis, 1955*a*). We have confirmed these findings in a patient of Dr. T. M. Chalmers.

Another approach to the problem has been to suppress endogenous corticotrophin by giving large amounts of cortisone, and then to measure the aldosterone secretion. Farrell and his group (1956*a*) have done this in the dog, and the results were very striking. After five weeks on 100 mg. of cortisone a day the secretion of cortisol and of cortisone, as measured in the adrenal venous blood, fell almost to negligible levels compared with control values, whereas aldosterone secretion was unaffected.

In man, under conditions of sodium depletion, Liddle *et al.* (1955) were unable to suppress aldosterone excretion by giving large amounts of cortisone ; and, conversely, Prunty and his co-workers (1954) did not suppress the 17-ketosteroid excretion in a patient with adrenogenital syndrome by giving large amounts of aldosterone.

To summarize the results of these experiments, it seems to have been fairly well established that aldosterone is largely independent of pituitary control, at least in the rat, dog, and in man. What, then, are the experimental conditions which will influence its rate of secretion? Firstly, there are a number of stimuli which seem to increase aldosterone secretion, and the first of these is salt depletion. Luetscher and Curtis (1955*b*) have shown that as the urinary sodium output falls, due to sodium deprivation, the aldosterone excretion rises to about five times normal. Liddle and Bartter have confirmed this finding and have stressed the fall in body-weight which accompanies the sodium depletion, due to loss of water.

Next, there is the effect of sweating, which causes a relatively greater loss of water than of sodium. Mach and his group (Falbriard *et al.*, 1955) at Geneva sweated a normal subject to the extent of his losing 1½ kg. body-weight. There was a rapid rise in aldosterone excretion, coincident with diminished urinary sodium excretion, but no change in the plasma electrolyte concentrations. These investigators also showed that potassium loading, which causes a loss

of sodium and water, is followed by a significant rise in the urinary aldosterone. Liddle *et al.* (1955) have confirmed this finding and have pointed out that the aldosterone excretion only rises when potassium loading causes a loss of sodium.

Mach also gave acetazolamide to normal subjects which caused a diuresis in which relatively more sodium than potassium was lost. The body-weight fell by nearly 1 kg. Again, there was a marked rise in aldosterone excretion. Whereas, in the one set of experiments these authors had given potassium, in the other they were depleting the body of potassium. The common factor was loss of sodium and water, in other words of body fluid.

Lastly, Farrell *et al.* (1956*b*) have shown that hæmorrhage in the dog increases aldosterone secretion acutely, as measured in the adrenal venous blood. Their latest experiments suggest that this rise in aldosterone secretion can be prevented if dextran is infused to replace the lost blood.

The common factor in all of the above experiments was a depletion of body fluid, whether caused by sodium deprivation, sweating, diuresis, potassium loading or hæmorrhage. The rise in aldosterone production did not appear to depend on changes in plasma sodium or potassium concentrations.

What are the conditions under which the production of aldosterone can be depressed? First, there is sodium loading. In an experiment which we made in co-operation with Dr. Geoffrey Walker we gave 20 grams of salt for two days to a normal subject. This was followed by a rise in the urinary sodium output and in body-weight, during which period the aldosterone excretion fell to nearly one-third of the control level. There were no changes in plasma sodium, potassium or protein concentrations, or in the urinary cortisol excretion. Forty-eight hours after discontinuing the extra salt, the body-weight and urinary sodium and aldosterone excretions had returned to the control levels (Garrod *et al.*, 1956*b*).

The second condition which appears to inhibit aldosterone secretion is severe potassium depletion. Thirdly, when excessive water retention is induced by giving pitressin tannate in oil and a high water intake, there is no rise in aldosterone excretion, although the plasma sodium concentration falls to very low levels (Beck *et al.*, 1955). Indeed, Liddle and his colleagues have reported that the aldosterone output falls concurrently with the increased sodium output at the height of water intoxication. This would seem to agree with Leaf's interpretation that the sodium diuresis of induced water intoxication may represent an adrenal response to excessive expansion of the body fluids (Leaf *et al.*, 1953).

It thus seems that aldosterone secretion is subservient mainly to the requirements of body fluid volume control.

Lastly, we have studied the diurnal variations of steroid excretion in normal subjects on four-hourly feeds of constant composition, in co-operation with Dr. J. D. N. Nabarro (Garrod *et al.*, 1956*a*). Whereas the cortisol excretion was very high during the first part of the day and very low at night, there were no significant variations in aldosterone excretion, despite large changes in the sodium and potassium outputs. These results provide further evidence of the independence of aldosterone from cortisol secretion, and indicate that there are other factors besides changes in aldosterone secretion, which will influence the rate of sodium excretion.

REFERENCES

Axelrad, B. J., Johnson, B. B., and Luetscher, J. A., Jr. (1954) *J. clin. Endocrin.*, **14**, 783.

Beck, J. C., Dyrenfurth, I., Giroud, C., and Venning, L. H. (1955) *Trans. Ass. Amer. Phycns.*, **68**, 205.

Falbriard, A., Muller, A. F., Neher, R., and Mach, R. S. (1955) *Schweiz. med. Wschr.*, **50**, 1218.

Farrell, G. L., Banks, R. C., and Koletsky, S. (1956*a*) *Endocrinology*, **58**, 104.

——, Rauschkolb, E. W., and Koletsky, S. (1955) *J. clin. Endocrin.*, **15**, 852.

——, Rosnagle, R. S., and Rauschkolb, E. W. (1956*b*) *Fed. Proc.*, **15**, 60.

Garrod, O., Nabarro, J. D. N., Simpson, S. A., Tait, J. F., and Walker, G. (1956*a*) Unpublished observations.

——, Simpson, S. A., Tait, J. F., and Walker, G. (1956*b*) Unpublished observations.

Leaf, A., Bartter, F. C., Santos, R. F., and Wrong, O. (1953) *J. clin. Invest.*, **32**, 868.

Liddle, G. W., Bartter, F. C., Duncan, L. E., Barber, J. K., and Delea, C. (1955) *J. clin. Invest.*, **34**, 949.

Luetscher, J. A., Jr., and Axelrad, B. J. (1954) *J. clin. Endocrin.*, **14**, 1086.

——, and Curtis, R. H. (1955*a*) *Ann. intern. Med.*, **43**, 658.

——, —— (1955*b*) *Fed. Proc.*, **14**, 746.

Prunty, F. T. G., McSwiney, R. R., Mills, I. H., and Smith, M. A. (1954) *Lancet*, ii, 620.

Simpson, S. A., and Tait, J. F. (1955) *Recent Progr. Hormone Res.*, **11**, 183.

Singer, B., and Stack-Dunne, M. P. (1955) *J. Endocrin.*, **12**, 130.

Malignant Hypertension and Hyperaldosteronism

By C. HOLTEN, M.D., and V. POSBORG PETERSEN, M.D.

1st Medical University Clinic, Kommunehospitalet, Aarhus, Denmark

A 13-YEAR-OLD girl was admitted with a history of increasing muscular weakness and convulsions, followed by rapidly developing malignant hypertension. The patient was very weak, emaciated and prostrate. No œdema was present. Blood pressure was 190/140. Retinopathy with bilateral papillœdema (6 dioptres) and exudates was demonstrated. She had polyuria, alkaline urine and slight proteinuria. Serum electrolyte analyses revealed hypokalæmia, slight hyponatræmia and alkalosis. The urinary excretion of aldosterone was found to be increased to 36μg and the excretion of cortisol was 72μg. per twenty-four hours. X-ray examination suggested an enlarged left adrenal. At the operation both adrenals were found apparently normal; a left adrenalectomy was performed. Post-operatively convulsions stopped and serum electrolytes reversed to normal range. However, the blood pressure and retinal lesions remained unaffected. Treatment with Ansolysen was initiated one month after the operation, and followed by reduction of blood pressure to 150 90 and complete disappearance of the papillœdema. Ansolysen was discontinued after a three months' course and following this the blood pressure remained at a level of 160/100. Serum electrolytes stayed normal, and urine output and concentrating capacity were normal. A striking clinical improvement with a weight gain of 16 kg. took place. Aldosterone excretion two and six months post-operatively was decreased to 11·8 μg. and 12·8 μg. respectively. Cortisol excretion in the same urine samples was reduced to 8·4 μg. and 20·7 μg.

Follow-up examination nine months post-operatively and four months after discontinuing Ansolysen showed the patient to be in good health. Blood pressure still 160/100. No papillœdema, but residual exudates were present. The urine contained a trace of protein. Renal function and serum electrolytes were normal.

Comments.—This patient presented some of the clinical and biochemical features which have been associated with primary aldosteronism, but also some ostensible differences. (1) Clinically: Malignant hypertension. (2) Pathologically: Absence of adrenal tumour or hyperplasia. Histology normal. (3) Biochemically: Slight but definite hyponatræmia.

We are much indebted to Mrs. S. A. Simpson and Dr. J. F. Tait, who carried out the determinations of aldosterone and cortisol, and to Dr. H. J. Whiteley, who did the histological examination of the adrenal gland.

Section of Urology

President—DAVID BAND, F.R.C.S. Ed.

[*April* 26, 1956]

DISCUSSION ON UROLOGY IN CHILDREN

Mr. J. J. Mason Brown (Surgeon in charge, Royal Edinburgh Hospital for Sick Children): *Lesions of the Anterior Urethra in Infancy and Childhood*

Lesions of the anterior urethra, though relatively uncommon in infancy and childhood, are none the less important because of the severe secondary changes they produce in the upper urinary tract. A knowledge of them is essential in the diagnosis of the cause of urethral bleeding or discharge and of some cases of urinary incontinence, infection and obstruction. The congenital lesions are of greater interest and importance than the acquired conditions to which the author made brief reference.

Congenital Anomalies

Hypospadias is a common anomaly, the definitive treatment of which is beyond the scope of this paper. In the newly born baby the absence of a normally situated urethral orifice and failure to find the abnormal orifice may result in the erroneous diagnosis of congenital absence or occlusion of the urethra. In some cases the abnormal meatus is stenosed and meatotomy or dilatation may be required.

Epispadias is a less common anomaly which is readily recognized. As it is not a lesion affecting the anterior urethra alone it will not be considered here.

Pinhole meatus.—This congenital condition may cause urinary difficulty, frequency or infection and may not be found until attempts are made to pass an instrument. It may affect the hypospadiac meatus. The external orifice is obviously pin-point in size and, while mild degrees may be treated by dilatation, care must be taken not to split the meatus and many require formal meatotomy. It has been described in association with ventral absence of the prepuce but in this condition may be due to the exposure of the meatus to ammoniacal burning and meatal ulceration. If the condition is not recognized the urethra proximal to it becomes dilated and there may be back-pressure effects on the bladder and kidneys, but this seems to require a very tight stenosis of considerable duration, for it has not been found in our cases.

Absence of the urethra.—Johnson (1923) states that absence of the male urethra is rare when the penis is present. He distinguishes two types (1) true absence when the urethral anlage has failed to develop, and (2) obliteration of the urethral canal after its formation. Dourmashkin (1943) found only 50 authentic recorded cases (46 male and 4 female) in living newborn babies and described 5 personal cases. In 32 cases there was no problem as the babies were stillborn or survived only a few hours. There was a high incidence of other congenital anomalies. In many distension of the bladder was so great that delivery was impeded. In 12 cases discovered later in life 7 had umbilical fistulæ, one vesico-vaginal fistula, 3 penile fistulæ and one a scrotal fistula. The development of the prostatic urethra from the urogenital sinus, the cavernous urethra from the genital gutter and the glandular urethra from the urethral plate necessitates two junctions between these different parts and occlusion occurs most frequently at these sites. In 55 living newborn babies the occlusions were as follows:

SITES OF URETHRAL OCCLUSION (DOURMASHKIN)

Glandular:		Membranous urethra	3
External meatus occluded by solid membrane	5	Prostatic urethra	1
Posterior wall of fossa navicularis	2	Entire urethra	1
Entire glandular urethra	11	Site not determined	1
Entire penile urethra	24	Female urethra	5
Part of cavernous urethra and meatus	1	Total	55
Cavernous urethra only	1		

The meatal opening was present in 6.

Dourmashkin (1943) treated his 5 cases by the forceful passage to the bladder of whalebone filiforms and a small ureteral catheter. This, despite the trauma involved, was followed by patency of the urethra. It appears, therefore, that occlusion is more common than absence

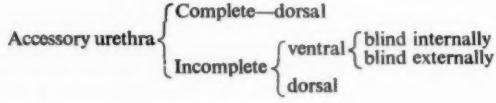
of the urethra and from the disastrous effects on the upper urinary tract of other obstructive lesions such as valves in the posterior urethra it seems likely that occlusion of the urethra has not been present throughout fœtal life or all babies in whom a fistula was not present would be born dead.

Stricture of the urethra.—Congenital stricture of the urethra, apart from meatal stenosis, is a very rare condition and I have no experience of it.

Diverticula of the anterior urethra are not so rare as Kretschmer (1936) makes out. In a survey of the literature he was able to find only 20 cases involving the anterior urethra. Ehrlich (1908) collected 32 congenital cases and in 1923 Johnson found 6 more but not all were in the anterior urethra and in some the site of origin was not stated. Geiringer and Zucker (1939) reported the case of a boy of 6 with a swelling in the upper scrotum which had become infected and the skin over it was necrotic. The child died from hydronephrosis but there was no evidence of obstruction in the urethra. The condition associated with megalo-penis is not very rare because two examples have been encountered recently. There is no doubt about the congenital nature of the lesions because they were present when the babies were seen on the day of their birth. As the two cases were almost exactly similar, except that the first had a larger lesion, a single description will suffice. At birth there was an obvious swelling on the undersurface of the distal part of the enlarged penis. The swelling extended from the undersurface of the distal penis into the ventral surface of the prepuce which appeared to be deficient on the dorsum. The urethral orifice was of normal size. On palpation of the swelling there was an immediate escape of clear urine from the meatus. When the baby passed water the swelling filled first and thereafter there was a dribbling stream of urine from the meatus. If the swelling were gently compressed when the baby passed urine the stream was more normal. In the first case there was an angular bowing at the proximal end of the swelling and palpation revealed that the corpus spongiosum was absent in the area of the swelling. Instrumentation revealed that there was no obstruction. With regular emptying of the pouch after urination infection did not develop and there was no back pressure effect on the urinary tract above. The first patient was investigated and the diverticulum was opened at operation. It had been my intention, because of the apparent lack of support for the urethra owing to the absence of the corpus spongiosum, to open the urethra proximal to the swelling on to the skin surface and to repair the hypospadias so made at a later date. However, after opening the pouch it was obvious that there was no obstruction in the urethra proximal and distal to it so the mucosa was separated from the skin, the portion in the prepuce was excised, one mucosal flap was excised and the contralateral flap of skin was removed, so that the mucosal and skin suture lines thus came to lie at opposite sides. The result was satisfactory both in reducing the size of the penis and in establishing normal micturition. Histology of the portion removed showed that—"the epithelium is of transitional type reduced in part of the surface to a single layer of cells. There is some chronic inflammatory cell infiltration under it". The absence of any obstruction distal to these lesions makes it difficult to explain their origin on an obstructive basis. Kaufmann (1886) believed that the cause was delay in the union of the penile and glandular portions of the urethra resulting in distension of the urethra which remained as a diverticulum when the urethra became patent. Suter (1908), on the other hand, believed that "the urethra originating from the genital furrow is covered with epidermis. A canal is formed which occupies the position of the future urethral canal. This canal is at first not closed on the side of the ventral surface of the future urethra, and there is a communicating bridge of epithelium connecting with the external skin. Normally this epithelial bridge is absorbed". It is the persistence of this bridge which gives origin to diverticula and to dermoids. Cabezas (1913) points out that the corpus spongiosum is totally wanting in the area of the swelling and that, therefore, the lesion can be explained only as an incomplete closure of the urogenital gutter or a disturbance in the development of the various tissue strata of the urethra due to an abnormal blood supply particularly in the spongy tissue.

Diverticulum not associated with megalo-penis is important because a concealed diverticulum may cause urinary obstruction (Gross and Bill, 1948) and infection and back pressure effects are likely to follow diverticula even in the penile urethra.

Double urethra in male and female.—Accessory urethra has been described by Fergusson (1945) in whose patient the dorsal accessory urethra terminated in the right seminal vesicle. Gross and Moore (1950) found 81 cases reported in the literature and added 2 of their own. They classified the condition in the male as follows:



In the 83 cases they found the following frequency of types:

TYPES OF ACCESSORY URETHRA

Dorsal, blind internal ..	48	Dorsal complete	19
Dorsal joining the urethra	12	Bladder to normal urethra in glans	1
		Ventral blind internal	3

When the accessory urethra is blind internally symptoms follow infection of the sinus and in one such case the accessory urethra was readily excised.

In complete dorsal urethra there may be two urinary streams sometimes or always, constant or slight incontinence or even no urinary symptoms when the condition is either found accidentally or the track becomes infected, as in the incomplete type. When the accessory channel joins the urethra it may lead to obstruction of the normal urethra by compression, as described by Higgins *et al.* (1951) and by Purcell (1949). Gross and Moore found that in the 19 recorded cases of complete dorsal urethra the site of the orifice was glandular in 4; coronal sulcus in 8; shaft of penis in 1; base of penis in 6. All except the glandular cases had an epispadias-like groove leading to the orifice.

I should like to record the case of a boy of 4 who had no symptoms by day but had always had nocturnal incontinence. The boy was referred to hospital because of occasional discharge from the undersurface of the dorsum of the prepuce. The prepuce was partly deficient on the dorsum but on the ventral surface there was a redundant fold like an apron. A gutter was clearly visible on the dorsum of the glans which led to an opening at the coronal sulcus under cover of the defective prepuce (Fig. 1). There was a normal external meatus from which he passed a normal urinary stream. The diagnosis of accessory dorsal urethra was made and investigation showed that the accessory urethra ran deep to the symphysis to reach the bladder (Fig. 2). Excision of the accessory urethra was followed by complete relief of the nocturnal incontinence.

←FIG. 1.—Complete dorsal accessory urethra in the male. Note normal meatus and epispadias-like groove leading to opening of the accessory urethra.

FIG. 2.—Catheter in the normal urethra with opaque medium beginning to pass through it. Accessory urethra completely outlined by opaque medium.→

Double urethra in the female is less common. Dannreuther (1923) described a female patient aged 50 in whom an accessory urethra led to a point above and to the right of the right ureteric orifice without any incontinence. De Nicola and McCartney (1949) described the case of a girl aged 6 in whom the accessory channel was obliterated by the injection of a sclerosant and the incontinence was cured. A girl of 5 years was seen because of constant wetness during the day, nocturnal incontinence and repeated urinary infections which recurred after adequate treatment. On examination there was an accessory opening posterior to the normal urethral meatus (Fig. 3). Intravenous pyelography revealed a double ureter on both sides and the diagnosis of ectopic ureter was made. A ureteric catheter was readily passed through the accessory opening and radiography revealed that the catheter was coiled in the bladder (Fig. 4). Cystoscopy showed only two normally situated ureteral orifices and confirmed the presence of the catheter in the bladder. The accessory urethra was treated by diathermy and after the second application it closed completely. The child was little, if any, better. Further examination showed that the accessory channel had closed. A close search failed to reveal the orifice of either ureter despite the fact that further intravenous pyelograms showed that both additional ureters continued into the pelvis (Fig. 5). Clinically, there was no doubt that the child must have ectopic ureteral orifices in addition. The right kidney was exposed, the upper small pelvis was opened and a ureteral catheter was passed down the upper ureter and emerged through the vagina. Right heminephro-ureterectomy was carried out and while the wetness became less it still persisted. A similar procedure was carried out on the left side and this time the ureteric catheter emerged through the urethra. Heminephro-ureterectomy on this side was followed by complete relief of the symptoms and a dramatic improvement in the child's outlook.

←FIG. 3.—Accessory urethra in the female. A ureteric catheter has been inserted into its orifice which opened posterior to the normal meatus.

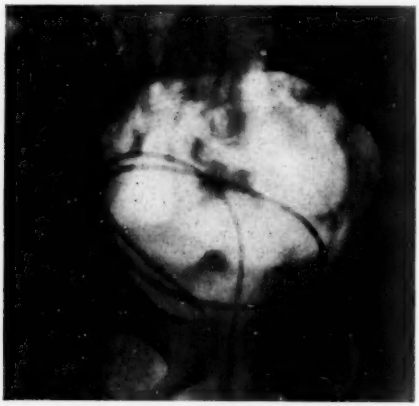


FIG. 4.—Catheter inserted into the abnormal orifice lying coiled in the bladder.

FIG. 5.—Intravenous pyelogram showing bilateral double ureters.

There is no doubt that a thorough investigation of such cases provides a great deal of interest, and surgical treatment results, in many instances, in cure of the conditions. The dangers of back-pressure effects and of infection are such that it is imperative to make an early diagnosis. All who care for the infant and child should be aware of the need for a full investigation of all patients who are not cured of their urinary tract infection by adequate therapy, or in whom the infection recurs without apparent cause.

REFERENCES

CABEZAS, M. (1913) *Amer. J. Urol.*, **9**, 413.
DANNREUTHER, W. T. (1923) *J. Amer. med. Ass.*, **81**, 1016.
DE NICOLA, R. R., and MCCARTNEY, R. C. (1949) *J. Urol.*, **61**, 1065.
DOURMASHKIN, R. L. (1943) *J. Urol.*, **50**, 747.
EHRLICH, P. (1908) *Beitr. klin. Chir.*, **59**, 193.
FERGUSSON, J. D. (1945) *Proc. R. Soc. Med.*, **39**, 198.
GEIRINGER, D., and ZUCKER, M. O. (1939) *Amer. J. Surg.*, **44**, 463.
GROSS, R. E., and BILL, A. H. (1948) *Pediatrics, Springfield*, **1**, 44.
——, and MOORE, T. C. (1950) *Arch. Surg., Chicago*, **60**, 749.
HIGGINS, T. T., WILLIAM, D. I., and NASH, D. F. E. (1951) The Urology of Childhood. London: p. 239.
JOHNSON, F. P. (1923) *J. Urol.*, **10**, 295.
KAUFMANN, C. (1886) *Dtsch. Chir.*, **50a**, 331.
KRETSCHMER, H. L. (1936) *Surg. Gynec. Obstet.*, **62**, 634.
PURCELL, H. M. (1949) *J. Urol.*, **62**, 748.
SUTER, F. (1908) *Arch. klin. Chir.*, **87**, 225.

Mr. Ashton Miller (Department of Surgery, Royal Infirmary, Bristol):

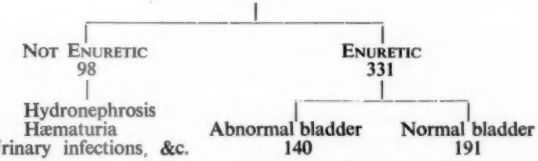
Cysto-urethroscopy of Enuretic Children

During the last five years we have performed cysto-urethroscopy on most of the enuretic children who were referred to the Bristol Children's Hospital. The examinations have been performed under general anæsthesia by either Mr. J. P. Mitchell or myself.

A total of 331 enuretic children have been examined and a further 98, who were not enuretic, had a cystoscopy done as part of the investigation of various other conditions. All cases of neurogenic bladder have been excluded, because they have some form of incontinence. For the purpose of this paper, enuresis is defined as micturition during sleep.

Of the 331 children, 191 had a bladder which was considered to be normal and 140 had varying degrees of a condition which we have called "bladder neck obstruction" (Table I).

TABLE I.—BRISTOL CHILDREN'S HOSPITAL 1950–1955



The criteria for this diagnosis are the presence of the thickened prominent muscle bundles of the internal muscle coat, known as trabeculation, combined with an internal sphincter muscle thicker than normal when palpated between a finger *per rectum* and the shaft of the cystoscope.

Some of the 98 "control" cases had trabeculated bladders, but none had a combination of trabeculation with thickening of the neck.

In the non-enuretic controls were found most of the conditions which in the past have been described as causes of enuresis, such as redness or apparent inflammation of the urethral mucosa, granulomatous changes (especially on the verumontanum), polypi and hillocks, a narrow urethra, and so on. Urethral folds adjacent to the verumontanum were visible in practically every male case: they were thought to be large enough to cause obstruction in only two cases and both of these had a very thick bladder neck. The verumontanum was found to be large in almost every male child and this is, like all the other things mentioned, a normal finding. The bladder neck itself was often a small opening in the cases of obstruction but this was by no means invariable and some cases of undoubted bladder-neck syndrome had a comparatively open neck without any "median bar" effect. We have found that the cystoscopic appearances of the bladder neck are not diagnostic in children, and have come to rely much more on the thickness of it, felt *per rectum*.

In both the normal and abnormal groups there were twice as many boys as girls (Table II). The abnormal group was divided into mild and severe, the latter being almost always those children who, in addition to enuresis, had marked frequency and urgency of micturition by day (Table III). The 54 severe ones have been treated by resection of the bladder neck;

TABLE II.—331 ENURETIC CHILDREN

	Normal	Abnormal
Girls	68	55
Boys	123	85

TABLE III.—140 CHILDREN WITH ABNORMAL BLADDER

Age	Mild	Severe
0–4 years	14	10
5–9 years	56	33
10–14 years	16	11

45 by transurethral resection and 9 by open transvesical operation. Of these, 30 can now be said to be quite normal by day and by night; 21 have been improved and 3 remain unchanged.

Thus we can say that about one-third of the enuretic children of school age that we examined had a degree of bladder-neck obstruction. It might, therefore, be thought that bladder-neck obstruction can cause enuresis because treatment of the obstruction will often stop enuresis as well as relieving the associated frequency and urgency, but it must be realized that at least two-thirds of enuretic children have completely normal bladders by any standards. Therefore there may be a factor responsible for enuresis which operates when the bladder is normal and also operates—probably more readily—when the bladder is abnormal. This investigation suggests that there is no abnormality of the bladder or urethra which can be said to "cause" enuresis, and that the presence of bladder-neck obstruction does not necessarily imply that the child is enuretic.

Mr. D. Innes Williams (Genito-urinary Surgeon, Hospital for Sick Children, Great Ormond Street; Senior Research Assistant, Institute of Urology):

The Congenital Neurogenic Bladder

On going through our records, I find that I have adequate data on 65 cases of congenital neurogenic bladder which were referred to urological opinion, and most of these have been under my supervision for some years. Because of the urological bias, the series does not contain a high proportion of those unfortunate infants who are born with a complete flaccid paraplegia, nor does it include those mildest examples of spina bifida with limb deformities but without serious bladder disturbance—though, in fact, some such children seen on the orthopædic side were enuretic.

TABLE I.—65 CASES OF CONGENITAL NEUROGENIC BLADDER REFERRED FOR UROLOGICAL OPINION

Myelo-meningocele ..	41	Males ..	27
Spina bifida occulta ..	10	Females ..	38
Sacral agenesis and scoliosis	14		

A myelo-meningocele in the lumbar or in the sacral region was the commonest primary lesion: the sac was sometimes ulcerated but more often deeply placed and fully skin-covered. There were several eccentric sacral myelo-meningoceles, and a number of examples of spina bifida occulta with myelodysplasia. True sacral agenesis has always, in my experience, been associated with a neurogenic bladder, but with other deformities of the sacrum, such as scoliosis, there has been more variability.

Spina bifida cystica of the cervical and thoracic regions is unlikely to be associated with cord damage, but otherwise there has been very little correlation between the type of bony deformity and the severity of the spinal cord lesion. Because of the common site of the deformity, the bladder dysfunction is almost always of the lower motor neurone type. However, the myelodysplasia usually extends over a greater length of the cord than the X-rays indicate: there is often hydromyelia, or a diastematomyelia, above the level of the spina bifida, and where the bladder centres in the conus escape complete destruction, there may be evidence of an upper motor neurone type of bladder disorder.

The great majority of cases in this series have had a partial paralysis of the lower limbs, with saddle anæsthesia, but in the purely sacral deformities the neurological signs have been curiously patchy, so that occasionally, even with an undoubted neurogenic bladder, there is a preservation of perineal sensation and normal rectal function. Because of this variability it is impossible to predict the exact type of bladder dysfunction from a study of either the spinal deformity or the neurological signs, and the cases have therefore been classified on purely urological grounds into three main types. I must emphasize that these are types, not stages, and there has been little tendency for a case to pass from one group to another.

The first type of bladder to be recognized (25 cases), is flaccid, thin-walled, without trabeculation and lacking any sensation of fullness. Post-mortem observations on infants dying of other causes, and not included in the present series, show that this type is peculiarly characteristic of the severe myelo-meningocele: in the lack of hypertrophy it contrasts with the usual autonomous bladder resulting from traumatic injuries, in which detrusor hypertrophy is often supposed to result from the activity of the intrinsic nervous elements. It may be that in the congenital cases there is a defect of the parasympathetic ganglia but we have not yet had the opportunity to investigate this point.

When the urethral resistance is very low, the urine dribbles out as soon as it enters the bladder, which is therefore never distended. Still, cysto-urethrograms in such children have a surprisingly normal appearance. When the resistance is a little greater, the bladder has a larger capacity and is expressible, but there is still no trabeculation, the bladder neck is flaccid, and the upper urinary tract is normal. There may be a residuum in the bladder after expression which will cause a dribbling incontinence, but a few fortunate children establish a balance between the powers of expression and the urethral resistance so that by periodic emptying of the bladder they can remain dry. This is an accomplishment which requires intelligence and practice, and it is seldom achieved until 8 or 9 years of age. The balance will be upset by an attack of cystitis, or by a large accumulation of fæces in the rectum. When cases in this group have presented with a large volume of residual urine, it has usually been possible to reduce it simply by sterilization of the urine, and evacuation of the bowel: these measures are most important and must be given a long trial before any surgical procedure is contemplated. Bladder-neck resection in these cases where there is no definite bar of tissue to resect is an unsatisfactory operation and is not likely to be helpful.

Some of the children with this type of bladder have suffered attacks of acute retention in which no urine could be passed at all, the bladder became tensely distended and caused severe colicky pain. This pain, which was presumably mediated by sympathetic nerve fibres, was not localized as arising from the bladder, but coincided with hardening of the tumour.

Such attacks have been precipitated by any type of operation, whether on the spinal cord, the urinary tract or the limbs, but have sometimes come on for no apparent reason.

Clinically somewhat similar to the first group, but cystoscopically very different, are the expressible bladders which show well-marked trabeculation, sacculation and a dilated posterior urethra, often with prominence of the bladder neck as a strong hypertrophied bar. The sacculations may at times reach the dimensions of diverticula, and be separately palpable but, provided the urine is sterile, complete expression without residual urine is often possible. The upper urinary tract may still be normal or show a very slight dilatation (13 cases). These trabeculated bladders are also subject to attacks of acute retention and they are a good deal more liable to urinary infection. When infection is present, the urine dribbles continuously, sometimes from the small spastic bladder, sometimes from a large residuum.

At times the trabeculated bladder is associated with severe upper urinary tract dilatation (23 cases, 6 dead); in cases with gross hydro-ureter, it appears that the dilatation has been present from a very early age and probably developed before birth. Reflux is common in such cases, but it is unlikely that it is the cause of the dilatation, since unilateral reflux is often seen in the presence of bilateral hydro-ureter. Dr. Edwards' cine film reveals that these big ureters are unusually rigid and exhibit a striking contrast with the idiopathic mega-ureters in their lack of movement. With such poor drainage of the upper urinary tract, infection is very liable to occur, and there is a progressive deterioration of renal function; as in traumatic paraplegia, uræmia is the common cause of late mortality and is the main hazard of those children who have survived the dangers of meningitis and hydrocephalus. The fact that the kidneys are failing does not, however, affect the degree of continence: all expressible bladders can at times be controlled, and there are several examples in this series of perfect control associated with a steadily rising blood urea. It might be supposed that where ve ico-ureteral reflux is present, manual expression of the bladder contents would inevitably lead to further ureteric dilatation: fortunately this does not appear to be the case and this method of management need not be discontinued on these grounds. Bladder-neck resection is much more likely to be helpful in lowering the urethral resistance in this type of case than in the former group.

One other form of bladder dysfunction is that in which some sensation of bladder fullness is present but—as in some cases of disseminated sclerosis—micturition is frequent, urgent and often uncontrollable (4 cases). Whereas the cases previously discussed may dribble urine in between expressions, these last children will often be incontinent of a large amount of urine at one time, though they never reach the stage of the true automatic bladder. Some residual urine is the rule, the bladder is usually trabeculated and the urethra dilated in the funnel-neck deformity. The upper urinary tract may not be severely affected. Cysto-metrograms show a sharply rising curve with desire to void at quite low volumes. Continence may be achieved in these cases by regular timed micturition, so that the urgent desire does not occur.

I have mentioned several times the possibility of improvement in the degree of continence, and it will be seen from Table II that a fair proportion of the children achieved sufficient

TABLE II

Approximately One-third of Cases Achieved Sufficient Control to Manage without Appliances

	All cases		Alive over 9	
	Total	Continent	Total	Continent
Males	27	4	14	3
Females ..	38	16	25	11
Total	65	20	39	14

control to enable them to do without any special appliances. This success is attained by good management rather than by improvement of the central nervous lesion, and it seems to have occurred more often without surgery than with it. Often no operation has been undertaken for the spinal lesion, but no case in this series has been improved by neuro-surgery and several were made worse. Deterioration of the neurological condition due to disproportionate growth between the vertebral column and the spinal cord, with consequent tension upon tethering bands has in the past received a good deal of attention, yet in my cases such deterioration has been exceptional and seldom attributable to this factor. Spontaneous worsening of the symptoms has occurred in 5 cases of sacral deformity without meningocele, causing an onset of urinary symptoms at the ages of 12, 18, 19, 25 and 54 years respectively. The spinal cord was explored in the youngest of these but there was no evidence of tension on the nerve roots or of bands binding down the cauda equina, and no useful surgery could be performed. In the others, growth had clearly ceased before the onset of symptoms.

Treatment.—This must be considered under two headings: the attainment of continence, and the preservation of renal function, for it will be found that measures designed for these two purposes may not coincide. Continence is not a very important problem in infants or very young children, and treatment for this may safely be postponed until 4 or 5 years of age. In cases where the bladder is expressible, our aim is to adjust the urethral resistance to the powers of expression, to obtain complete emptying of the bladder with each act and to see that the acts are performed with sufficient frequency to maintain dryness. When expression does not altogether eliminate the dribble, certain simple appliances may be used in the male: the simplest of these, the penile clip, is difficult to apply to a small penis, and a circumcision is almost always required to enable it to be used at all; after the age of 9 or 10 it is sometimes fairly satisfactory provided that it is not left on at night. With more serious degrees of urinary incontinence, the portable urinal is probably the best appliance for the male. In the female, I have had very little success with external appliances, and operative diversion of urine may well be required, but in any case where there seems to be any hope of improvement it is rash to undertake any irretrievable surgical step before the age of puberty.

The preservation of renal function may demand a much earlier intervention, and persistence of infection or severe hydro-ureter will indicate the need to secure better drainage of the urinary tract. In the male, and in the very young female, bladder-neck resection and other measures to reduce the urethral resistance should first be undertaken, but it must be admitted that the progressive deterioration of renal function is not always avoided. The use of ileal loops is still rather in the experimental stages, though I feel certain that the cutaneous ileo-ureterostomy will prove a most satisfactory solution in the case of the girl with hopeless incontinence but normal ureters. The cases with hydro-ureter, however, have already impaired renal function and I fear that we will find that in such circumstances the introduction of an ileal loop into the urinary tract will have serious disadvantages. We may well find that suprapubic cystostomy in the male, and cutaneous ureterostomy in both sexes, still have a place.

Dr. David Edwards (Institute of Urology, University of London):

Cine Radiography of the Congenital Neurogenic Bladder

Image intensification produces a much brighter fluoroscopic image at a lower X-ray dosage and makes cine radiography possible without subjecting the patient to excessive radiation. All micturating cystograms at St. Paul's Hospital are now carried out with an Image Intensifier and a 35 mm. cine camera. By this means it is possible to study at leisure both the anatomy and the physiology of the region under examination.

The patient is asked to empty the bladder, which is then filled by means of a urethral catheter with 30% diodone, and a cine film is obtained both before and during micturition in the antero-posterior and both oblique positions. For routine cystography a 20–30% barium suspension is an excellent and cheap contrast medium, but owing to the frequent occurrence of ureteral reflux and residual urine, it should not be used in this group of patients.

The great majority of cases of congenital neurogenic bladder have gross defects affecting the sacral or lumbar vertebræ with or without a meningocele.

The anatomical changes seen in the cysto-urethrogram have been well described by Ney and Duff (1950). The bladder may be large or small; the small contracted bladder with greatly thickened and hypertrophied walls results in irregularity of its outline in the cystogram accompanied by sacculation and possibly diverticulum formation. Characteristically it has a pine tree shape—the bladder tapering towards its apex (Fig. 1). On the other hand the bladder may be large and show little or no trabeculation (Fig. 2).

The posterior urethra frequently contains urine in the resting stage prior to micturition. Urine may only extend for a short distance along the posterior urethra stopping well proximal to the external sphincter (Fig. 3). In other cases the dilatation of the posterior urethra may be much more marked and extend down to the external sphincter, tapering to a narrow point at this level—the so-called "funnel urethra" (Fig. 4) first described by Burns (1917). The wide bladder neck described in enuretic girls by Fisher and Forsythe (1954) gives a similar appearance (Fig. 5) but bladder contraction is normal and there is no evidence of a neurological lesion. [A film demonstrating this anomaly was shown.]

The external sphincter in the neurogenic bladder is not infrequently contracted so that only a narrow stream of urine is seen at this site.

Vesico-ureteral reflux in which urine enters either or both ureters from the bladder is common and the whole length of the dilated and tortuous ureters may be demonstrated together with the renal pelves and calyces. In all the cases of neurogenic bladder associated with reflux that I have examined ureteric contractions have been absent. This may possibly be the result of severe infection but it may also be the direct result of the neurological lesion.

TRACINGS FROM CINE FILM

FIG. 1. — Pine tree bladder with ureteral reflux.

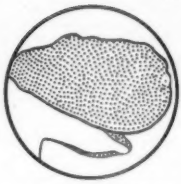


FIG. 2.—Large bladder, little trabeculation. Narrow external sphincter.

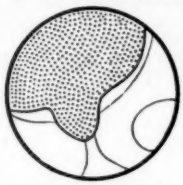


FIG. 3.—Filling of posterior urethra at rest.

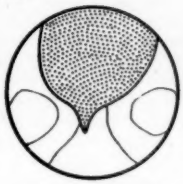


FIG. 4.—Funnel urethra.

FIG. 5.—Wide bladder-neck anomaly.

These are in contrast to cases of mega-ureter where ureteric contractions are the rule. (Demonstrated in the cine film.)

One of the most striking features in this series is the change in the mechanism of micturition. As was shown on the film, normal micturition is initiated by a sharp downward movement of the bladder and relaxation of the external sphincter followed by a smooth uniform contraction of the bladder wall, rather like a slowly deflating balloon. With the exception of one doubtful case, this normal contraction is entirely absent in this series. Voiding is produced by abdominal or manual expression. Upward and downward movements of the bladder produced by the action of the levator ani, the diaphragm, and the anterior abdominal wall are seen to persist throughout micturition and are not confined to the onset. Symptoms such as urgency and precipitate micturition, together with cystometry readings, indicate that some bladder contraction can occur in these patients when the bladder is over-distended with fluid, but these contractions have not been demonstrated in the film presumably because this level of "critical stretch" was not reached.

The writer wishes to thank Mr. D. Innes Williams who suggested the investigation and who referred the patients for examination.

REFERENCES

BURNS, J. E. (1917) *Surg. Gynec. Obstet.*, **24,** 659.
FISHER, O. D., and FORSYTHE, W. I. (1954) *Arch. Dis. Childh.*, **29,** 460.
NEY, C., and DUFF, J. (1950) *J. Urol.*, **63,** 640.

Mr. Hugh Donovan drew attention to the anomalous behaviour of the external sphincter. It seemed difficult to understand how it was that it maintained its tone when the cauda equina was destroyed.

Mr. A. W. Badenoch said that he was interested in the rather new conception expressed by Mr. Ashton Miller that enuresis was due to an obstruction of the bladder neck. This rather cut across previous conceptions. Most medical treatments had been designed to stimulate contraction of the bladder neck rather than to lessen it. The evidence which had been produced of the existence of obstruction was still a little slender. The thickening felt by the finger against the cystoscope was of no value in his experience. He had never been able to convince himself even in cases where there was other obvious evidence of an obstruction that he could feel anything with his finger. He would like to have a little more evidence about this obstruction of the bladder neck in the cases which Mr. Miller had mentioned and to know in which age group successful treatment had been applied. Quite a number of enuretic cases recovered without any great attempt at interference or perhaps in spite of it.

Mr. Howard G. Hanley said that he would like to know a little more about this bladder-neck obstruction. Many children were referred to him by the pædiatricians because of recurrent infection. He thought that bladder-neck obstruction was relatively common in these cases, but he was puzzled to know what was normal and what constituted obstruction when seen through the cystoscope or urethroscope. He had cystoscoped one child and thought there was bladder-neck obstruction with a markedly raised "median bar", but when three weeks later arrangements were made for the medical artist to draw this condition, it had disappeared.

Mr. E. W. Riches said that he had been impressed by the number of children with enuresis who had spina bifida occulta; he believed that it was not entirely fortuitous. He had operated on quite a number, and some had been cured. The operation consisted of decompressing the cauda equina by excising the bifid spine and removing the band of thick fibrous tissue which was found beneath it.

A member asked if Mr. Riches had tried the simple method of stretching the membrane by injecting saline into the spinal canal, which sometimes produced a remarkable result.

Mr. Riches said that he had tried this method but without any success. Although he did not doubt the existence of a membrana reuniens the fibrous tissue to which he was referring filled up the gap where the spine ought to join and formed a very firm mass.

Mr. J. J. Mason Brown said in discussion that most of the questions were concerned with enuresis of which he had little experience. In his hospital they had a physician who was very interested in this subject and most of the cases went to him first. There was also a child psychiatrist who was interested in it and he could only assume that they cured the vast majority of the cases because he saw very few. He had shown one example with the double urethra and two ectopic ureters and one would hardly expect a physician or a psychologist to deal with them.

Mr. Ashton Miller said that the endoscope used had a foroblique telescope with three different sizes of shaft corresponding to 12, 14 and 16 (French).

In reply to Mr. Badenoch he said he had been careful to suggest that enuresis was *not* due to this condition of bladder-neck obstruction, he thought it was only associated with it. Enuresis could be associated with an absolutely normal bladder and with normal micturition during the daytime. He felt sure than when resecting these bladder necks he was treating a condition in which enuresis might or might not be present. There had been 3 cases of children with trabeculated bladders who were awakened two or three times a night to micturate but who were not enuretic. He was sure that there must be something else which caused the enuresis but what it was he did not know.

It was difficult to give convincing evidence of obstruction in these children. The trabeculation was carefully assessed with the bladder adequately filled; the neck was always palpated with the cystoscope in the urethra and the bladder empty. In the normal child one could feel something at the bladder neck like a small piece of string. When thickened it was of a somewhat softer consistency and felt like muscle.

It was assumed that there must be obstruction because of the hypertrophy of the internal muscle coat, visible as trabeculation. This assumption was made because one knew that it happened in the adult when the outlet of the bladder was obstructed. The cystometrogram showed a hypertonic bladder with a rapidly rising curve. Occasionally, in the more marked cases, there was residual urine and there was diverticulum formation. The bladder was always found to be hypertrophied when a diverticulum was present. These cases occurred in all age groups right through life and there was no apparent difference between the child who had a thick-walled bladder and the adult aged 35 with frequency of micturition who was found to have a hypertrophied bladder and who was improved by transurethral resection; such a patient often gave a history of frequency in childhood and said that he "had always had a small bladder". He (Mr. Ashton Miller) would admit that this was not proof that there was obstruction and could not produce any better evidence; there certainly seemed to be a condition which he had called "obstruction of the bladder neck" for want of a better name.

A question was asked regarding the danger of sterility. One knew that the adult man undergoing a transurethral resection or a prostatectomy was likely to be sterile. One found, however, that expectations and fears in this matter had not been realized in younger patients, because a number of resections had been carried out on teen-age boys and young adults with this condition. The power of ejaculation had been lost for a time but there had not been one who had not regained it. The longest time, in his experience, that it had been lost was nine months. In the young man the fear appeared to be groundless for there was always enough muscle tissue left behind to produce contraction of the internal sphincter. He did not, however, think this happened in the older man because much of the muscle was then replaced by fibrous tissue.

He always understood that the incidence of spina bifida occulta was the same in enuretic as in normally micturating children (Stalker and Band, 1946). In the absence of a demonstrable neurological lesion he thought it could not be responsible for enuresis as an isolated symptom.

Mr. Hanley's question had dealt with the variability of the bladder neck and he agreed with what he said. One could not go by the appearance of the bladder neck at cystoscopy and make deductions from that. He had had the same experience when children had been cystoscoped on more than one occasion and the appearance of the bladder neck had been different; palpation by a rectal finger more accurately demonstrated thickening.

Was Dr. D. Edwards certain that the levator ani muscles actually were contracting? It seemed to him that the bladder was pushed down by contraction of the diaphragm when the child strained at the end of a deep inspiration and rose up again when the pressure fell during expiration. The flow of urine seemed to correspond with this. Were not the levator ani muscles atonic in some of these children?

REFERENCE.—STALKER, H., and BAND, D. (1946) *J. ment. Sci.*, **92**, 324.

Mr. D. Innes Williams said that it seemed that the cause of the enuresis depended entirely upon the particular instrument of investigation which was employed, but as long as the clinician treated the cases according to his own beliefs the results seemed to be magnificent.

With regard to Mr. Ashton Miller's remarks, he personally would not accept the presence of mild trabeculation of the bladder, admittedly common in children with frequency and enuresis, as indicative of bladder-neck obstruction; for this diagnosis he thought that there must be either residual urine or upper urinary tract dilatation as well. On these criteria bladder-neck obstruction was rare in boys, and exceptionally rare in girls; if a mild degree of the same disorder were responsible for enuresis, the same difference in the sex incidence would be expected.

In reply to Mr. Donovan's question about spasm of the external sphincter, he thought that this was only important in upper motor neurone lesions, which were very unusual in congenital disorders.

Dr. D. Edwards, in reply, agreed with Mr. Ashton Miller that the levator ani might be atonic in this group of patients but, as the cine film showed, the ascent of the bladder was a sharp, abrupt upward movement very suggestive of an active contraction of the levator ani. It was very similar to the ascent which occurred normally when a patient was asked to stop micturating. If this was a passive movement in response to decreased abdominal pressure, he would have expected it to be a gradual ascent.

Section of the History of Medicine

President—Sir Zachary Cope, M.S., M.D., F.R.C.S.

[*April* 4, 1956]

The Management of Lunacy in Seventeenth Century England. An Investigation of Quarter-sessions Records

By A. Fessler, M.D., L.R.C.P., M.R.C.S.

Miss K. Jones remarked in her book "Lunacy, Law and Conscience, 1744–1845" that for the whole period with which she was dealing only little material concerning the management of the insane exists. She explained this scarcity of information by the fact that no accounts were kept of the insane inmates of the private mad-houses, houses of correction and work-houses. The situation is different with regard to the seventeenth century and to the first two decades of the eighteenth century, because quite a large amount of information can be found in some of the so-called Local History Documents, especially in the quarter-sessions records in which most of the work done by the Justices of the Peace is recorded. These officials had to concern themselves for various reasons with many of the cases of lunacy that occurred among the lower and middle social classes. Being magistrates, the Justices had to deal with breaches of the peace, either actually committed or threatened by the insane. They had to decide various medico-legal problems connected with lunacy; among these was the difficult one as to how far lunatics can be held responsible for their deeds. The Justices, in their capacity as principal administrators of Local Government, had to supervise the administration of the Poor Law Act, which was passed in 1601 (43 Eliz. c. 2), as it was carried out by the parish officers. Being unable to work, lunatics were eligible for poor relief, but before an allowance was granted, the authorities had to be satisfied that the nearest relatives of these persons were, financially or otherwise, incapable of maintaining them. The upkeep of an insane person put a heavy financial burden on his family, especially if his type of lunacy made it necessary that he should be kept closely guarded. Therefore families which, strictly speaking, were not poor, tried to obtain an allowance from their parishes.

Another reason why the Justices often had to concern themselves with the management of lunacy arose from the fact that once the houses of correction had been established (in accordance with an Act of Parliament passed in 1609), it soon became the practice to admit dangerous lunatics to these institutions; no person, however, could be admitted to such a house, or released from it, without an order issued at a quarter-sessions.

The medical writers of the seventeenth century knew only two types of lunacy, melancholy and madness; synonyms for the latter type were mania and fury. They all stressed the necessity of the proper management of the mentally ill. Burton in his "Anatomy of Melancholy" even put "recreation and exercise before physicks". He suggested that melancholic persons should be entertained with "mirth and merry", should be taken on a journey, &c. Willis (1685) only partly agreed with these suggestions, because he was of the opinion that in the management of melancholic persons harsh measures are also sometimes necessary, because "the affectations of the mind—are either to be appeased or subdued by others opposite". As examples he suggested that "to desperate Love ought to be applied or shewed indignation and hatred; Sadness is to be opposed with the flatteries of Pleasure, Musick —or also pannick terror". For the management of the mad, general opinion was in favour of very harsh treatment. According to Willis, it was necessary to resort to "threatening, bonds or strokes as well as Physick". He was convinced that "for the curing of mad people, there is nothing more effectual or necessary than the reverence or standing in awe of such as they think their Tormentors". McMenemey (1955) has pointed out that before one condemns this method of management, one has to remember that in many cases restraint was necessary for the sake of the lunatic persons themselves. Willis' statement, however, makes it clear that harsh treatment of the insane was advocated not only for the sake of restraint, but also because it was thought that punishment was necessary and beneficial.

This paper is mainly based on an investigation of Lancashire quarter-sessions records,

of which records only very few have been published so far. Reference to the management of lunacy can be found in the sessions rolls, in the orderbooks and in the petitions which were presented to the Justices. The entries in the sessions rolls and in the orderbooks contain, as a rule, only few details; it is stated that such and such a person was found to be distracted or to be lunatic, and the decision of the Justices as to what was to be done with him is given. The petitions are a much richer source of information, because the petitioners, who were either relatives or representatives of the parish, being anxious to obtain a favourable decision, informed the Justices about various details, e.g. about the age of the insane person, about the type and the duration of his illness, about the attempts made to keep him confined. Quite frequently there are also references to the economic conditions of the relatives of the lunatic person. The petitioners used a large number of expressions to describe the mental state of the person on whose behalf they presented the petition. The persons are described as being mad, melancholic, lunatic, frantic, raving, furious, frensic, crazed, hunted, *non compos mentis*; or it is stated that they are distracted in their mind, in their senses or in their wits; or that they are suffering from a trouble in their brain. Of the various medical terms which appear in the petitions, the term "melancholy" is most often used, very likely because this diagnosis was one of the favourite diagnoses of the period. As the petitions were written by lay people, it was inevitable that medical terms were not always used correctly. In a petition, presented in 1654, a description of a melancholic man is given which seems to correspond with the current idea of this form of mental illness. Some parishioners informed the Justices that a man

> throu falling into a sudden and sad Melancholie never since has been able to follow any calling —that pitifully he would walke upon the greene night after night not come in any house or take meate but by much force—by continuance in this course and by want of dressing washing and looking too his head was so festered and corrupted (the like seldone heard of) that the grubbs had almost eaten in to his braine all over his head.

The petitioners, who were asking for an allowance for the man, went on to say that they

> forced him to a house provided a woman to dress and to take care of him his head is somewhat better though not his disease and it is fearful he wilbe lost through want of subsistance (Q.S.P. 102/4).

In other petitions, however, melancholic persons are described as being "unruly", or it is stated that they are "hard to be governed".

When a petition was presented on behalf of a non-dangerous lunatic person, the Justices were, as a rule, merely asked to grant an allowance or to increase a previously granted allowance which had become inadequate. In 1673 for example the widow of a schoolmaster protested against a decision of the parish officers to reduce the allowance for her daughter who

> hath beene Melancholick in a verie strange manner and sadlie distracted to the great wonder of all her neighbours (Q.S.P. 409/1).

The parish officers had to take charge of those lunatic persons who had no relatives to take care of them. In 1626 the Justices ordered that the churchwardens and overseers of the poor of a parish had to take care of a woman who is

> lunaticke and is not of Abilitie to mayntayne and keepe herselfe and forasmuch as this Court is informed that neyther her parents nor any of her Kinsfolke are of Abilitie to mayntayne and keepe her (Q.S.P. 26/57).

Or in 1674 the overseers of a parish were ordered to provide

> a lunatic person called Jack a Cobbs with a coate a shirt and cap and other necessaries (Q.S.P. 425/27).

Insane persons who had become the charge of the parish were "tabled" with one of the parishioners and, consequently, one can find in parish accounts an occasional entry like that in the account book of the Manchester constables. In 1646 they made a note that they had paid 3s. to a man "for Diet" of a woman "being distracted" (Earwaker).

Petitions concerning the mad, the raving, the frantic, the frenzied, in one word the dangerous lunatics, were presented either by relatives who could no longer deal with the situation, or by neighbours and other parishioners who felt themselves being threatened. Very often in these petitions the Justices were told in the short and tense phrases so typical of seventeenth century style, about the harm which the lunatics had already done—or were liable to do—either to themselves or to others. The Justices were also informed about the measures taken so far to see that the lunatics do not "spoyle themselves or others". For example, the petitioners reported that they had kept their insane relative chained or bound in a house, that they had to call in neighbours to help or that they had been forced to hire special guards.

The Justices had three possible methods of dealing with these cases. They could decide

that the nearest relatives were capable of looking after the insane. An example is the decision they reached in 1653. They had been informed about a woman who

> is and hath beene distracted of her senses and hath for a long tyme beene suffered in that distracted condition to wander and begg to the great terror of the people of this commonwealth

and they decided that the husband of the woman should

> give security to provide for her and keepe her from doing mischeeffe or to be bound over (Q.S.P. 79/2).

Several times the Justices granted a special allowance to hire a person to look after the insane. They did so for instance in 1661, when a man applied for relief on behalf of his sister, "a poore distracted woman". He told the Justices that his sister had been able to work

> until it pleased God that she fell distracted and is troubled by a virulent lunacy in which she hath continued pulling herself and her apparell in pieces to the great danger not only of spoyling herself by some sudden death but to the danger of the neighbours.

He mentioned that he is

> compelled sometymes to bind her and to sitt a keeper or some friend to look for her to prevent further danger (Q.S.P. 215/1).

In 1681 a weekly allowance of 12 pence was granted to a man who complained that

> his wyffe is extraordinary troubled with a Mellancholic Distemper in soo much that shee is in danger to distroy herselfe if shee should be left in the house for the space of halfe an hour allone and he hath a Child that is About A month above halfe a yeare old and he can not leave his wyffe and go to his worke unlesse he hire Anable person to stay and looke to his wyffe for feare shee distroy herselfe (Q.S.P. 537/6).

In 1684 a man informed the Justices that he was in need of relief because his son

> havinge beene distracted now for eight yeares soo that he hath beene constrained for the said tyme sometymes to hire three men to attend upon him but never under one (Q.S.P. 587/13).

The second possibility was to order the parish officers to provide the means for keeping the insane person under guard. If the Justices regarded the case as a breach of the peace and regarded the lunatic as a "disorderly person", such an order was sent to the constables. In 1627 an order was issued to the officers of a parish to "make provision for Maytenance and habitation" of a man

> who is to bee lunaticke and out of his Senses during such tyme as hee shall contynue lunatick so that he may be kept close and not comitt any misdemeanour (Orderbook, 1627).

In 1641 the "24 men of a parish" (the vestry men) were ordered to take care of a man who according to the information given by his wife to the Justices

> hath fallen by gods Judgment and Visitation into a lunatic frensie and distraction of his witts and senses—hee lyinge bound in Cheanes and ffeathers—every of the neighbours fearfull to come neare into him in his fitts often befallinge upon him both night and day in most fearfull terible shrikes and shoutinge, saveinge his owne naturall father beinge an old and aged man of Threescore and three Yeares of age who often adventures himself into him to keepe him in some awe and subordination (Q.S.P. 1/245).

In 1651 a woman presented a petition on behalf of her husband who

> hath fallen into a Lunacy and Violent distraction about the space of 5 or 6 weekes agoe and soe doth Continue, he haveinge been distracted before this, but not in soe violent a manner, and upon the last presse hee was taken to serve—and it pleased God that hee fell into a extreame Lunacy, was greivously beaten wounded and turnd home, where hee doth remayne bound up in Iron Chaynes at this present, haveing nothing to releife himselfe withall, but as your peticioner beggs the Alms of Charitable people, nor any to looke to him—beinge lockt to a post.

The woman asked for an order to the constables "to take some Care over him that hee may bee easd of his Chaines", and the Justices decided that the churchwardens and overseers had "to take care and to provide for him" (Q.S.P. 51/1).

In 1668 the Justices issued an order that a widow who is

> a poore distracted woman and hath lately pulled out one of her Eyes and is wandering about—and offers violence to her owne Children may be kept by some person to be appoynted by the overseers of the poore when she shalbe found (Q.S.P. 319/23).

All the parish officers were able to do when they received such an order, was to find somebody in the parish who was willing to take the lunatic person into his house and keep him there in safety. The way this was done becomes apparent by a complaint lodged in 1682 by a man who did not receive his promised payment. He complained that the overseers did not pay

> for the maintenance of a Lunatic who now remains in Chaines at his house and is likely to be starved for want of food.

The overseers were ordered to pay 7 pence weekly "for the keeping of the lunatic" and in the following year the allowance was raised to 12 pence per week (Q.S.P. 570/9 and Q.S.P. 586/9).

The third possibility was to send those dangerous lunatics who no longer could be kept in safety in their parishes, to the house of correction. Sometimes the relatives themselves asked the Justices to issue such an order. For example in 1684 a father asked the Justices to send to the house of correction his son, who

> hath lately become lunatic and so Melancholick so that he can not rule him (Q.S.P. 593/18).

In 1708 the Justices granted an order for the admission to the house of correction of a woman who was described by her husband as being "a daily nuisance to her neighbours". The man explained that he was forced to ask for the order because

> he had done what he can to help her both by Doctors and by chaining her (Q.S.P. 983/12).

Looking through the records which deal with the admission of insane persons to the house of correction, one gets the impression that the Justices used this method not as a routine method. They seemed to have considered each case and it was only as the last resort that a lunatic was sent to the house of correction. In 1684 for example they decided that a lunatic woman should only be sent to this house "unless her brothers will take and relieve her" (Q.S.P. 594/3).

In 1688 the Justices explained why they had decided to send a man to the house of correction. They declared that this man

> in his lunacy was tabled with a parishioner and was kept and chained—but in his lunacy broake of his Chaines and went to a house and pulled down the slates and spoyled the goods and but for that Neighbours came in would have burnt the house and is a person not fitt to go loose (Orderbook, 1688).

A few records give one the impression that occasionally the Justices might for humanitarian reasons have hesitated to send an insane person to the house of correction. For instance in 1669 they added to an order concerning the admission of a lunatic woman to the house of correction the remark that the woman should be "kept there without whippinge" (Q.S.P. 331/5). In 1671 they left the decision of what to do with a man who was "in a distracted condition" to the parish officers; they could either leave him in the house of correction or convey him "to Bedlam if hereafter it shall be found requisit to send him thither" (Q.S.P. 391/32). This record is the only one which refers to Bedlam, London's mental hospital. Another record, however, shows that the man was kept in the house of correction. One reason why lunatics were not sent more frequently to the house of correction was perhaps the fact that the upkeep of an inmate in this institution was rather expensive. Although the Justices made an order out in every case as to who was responsible for these expenses, either the relatives of the insane person or his parish or both parties together, the masters of the house had difficulties in collecting the payment and were forced to complain to the Justices; occasionally, they even threatened to discharge the lunatic, if no payment was made. One of these complaints throws some light on the conditions under which the insane inmates of the house of correction in Preston were kept. In 1674 the master of the house informed the Justices that

> a single woman being a distracted lunatic was Comitted to the house of correcton there to be set on worke and kept with reasonable dyett and moderate correcton till shee should be thence delivered by Order of Law and that shee having ever since remained in the house, hath beene in such continuall distraccon that shee could not be broght into any capacity to be fit for any worke your peticioner having for all the time found her meate and drinke at his owne Charge and by reason of her great distemper hath bin put to much trouble and charge in attendance on her and that all her Cloathes are worne and spoiled so that shee hath not wherewith to Cover her nakedness.

The Justices ordered the parish to which the woman belonged to pay "25s. for the yeare past and £4 a year" (Q.S.P. 420/27).

A few more records are extant which provide information about the treatment of the lunatics in the house of correction. Miss Tollit, who has written on the history of the Lancashire house of correction in Preston (it was established in 1620), has published several bills which had been presented by the master to the quarter-sessions after repairs had been carried out at the house. A bill from the year 1672 contains the following item:

> For mendinge the prison bedds in the dungon which weare brokne with a distracted man.. 8s.

A similar entry is to be found in a bill presented in 1703:

> The Charge of making 4 Boxes in the Lower prison for ye securing of made people with good planks £10
> (Q.S.P. 987/42).

It was also left to the Justices to decide, without the advice of a medical expert, whether

the mental condition of a lunatic person who had been confined to the house of correction for some time had improved sufficiently for him to be released. In 1672 the Justices gave an order for the discharge of a lunatic inmate from the house of correction, after a mother had explained to them about her son who

> about halfe a yeare ago out of some trouble of minde and discontent fell into Melancholly and some Distraccon and thereby becoming unruly was sent to the howse of Correcon at Preston where he hath ever since remained, and is now cleare of his distemper and fit to goe at large without any danger of doing harm to himselfe or others (Q.S.P. 395/20).

Equally, the Justices were asked to intervene and issue an order for readmission to the house of correction, when one of the discharged persons had a relapse. They did so for example in 1663, after they had been informed that an old woman, being discharged from this house, had

> returned to her former evill course is agen distracted of hir senses and hath done severall abuses (Q.S.P. 243/33).

The writers of legal commentaries such as Dalton (1635), Coke (1648) and Hale (1778) were unanimously of the opinion that lunatics cannot be held responsible, either in criminal or in civil cases, because, as Dalton said, they "have not knowledge of good and evill". Lunacy was defined as "an involuntary ignorance", in contrast to drunkenness which was regarded as "a voluntary ignorance", for which no excuse can be pleaded. One has to note, however, that Dalton, whilst being convinced that "a mad man is only, and enough punished by his madnesse" thought that insane persons have to be severely treated on account of their behaviour. He stated that, as a father can chastise his child (up to a certain degree), or the governor of a prison has the right to punish his unruly prisoners, so may punish "any man his kins man that is madde".

Those of the Lancashire records which deal with medico-legal questions connected with lunacy, show that the Justices acted in accordance with the rules laid down by Dalton and others. In 1685 they ordered the officers of a parish to take charge of a woman who had been "visited with a deep Melancholy" and had become "very troublesome to deal with". They also arranged a wardship for her, because they asked that the overseers of her parish should "order the affairs" of the woman who "had estate left her from her husband about forty shillings worth" (Q.S.P. 597/7).

In 1669 the Justices granted relief to a woman whose daughter

> was brought to bedd of a bastard child, and being simple Lunaticke was of no discrecon to father the child (Q.S.P. 344/6).

In 1654 a miscarriage of justice was rectified by the Justices after they had been informed of a man who

> about six weeks agoe was committed to the common gaole for want of suerties for good behaviour upon information that he broke 3 panes of glass—now it is that the outrage and offence was committed by him by reason of his lunacy and distraction and not of any other bad carriage and behaviour (Q.S.P. 108/5).

The decision of the court was that the man should "be set at liberty at his house".

In contrast to the Lancashire records, considerable parts of the quarter-sessions records of other counties have already become available in print; so far only entries in the sessions rolls and in the orderbooks have been published. Examination of these records shows, as was to be expected, that the management of lunacy in other parts of England was similar to that outlined for Lancashire. The information provided by the Lancashire records, however, is more detailed, because a large number of petitions are still available. The following few entries of the published records from other counties have been chosen for quotation.

Somerset

In 1613 the Justices decided to send an insane woman to the house of correction after she had set fire to a house, and added to the order that the woman

> ought to be kept there in such a manner as the law requires for such dangerous and disorderly persons.

In 1622 it was decided that a man

> shall have £9 yearly out of the benefit of the tenement of his brother a weak mazed man not able to govern himself.

In 1637 the master of the house of correction released a man, described as "a lunaticke

and disorderly person", because he did not receive any payment for his upkeep. The Justices decided that the man had to be readmitted and that the parish had to pay

> if it appeare that he hath no goods of his owne wherewithall to maintaine him there.

Warwickshire

In 1655 a girl was brought before the quarter-sessions after a complaint had been received that she

> pretending herself to be distracted goes peddling up and down disturbing the peace and is abusive and troublesome.

She was sent to the house of correction, after the Justices had decided that her

> abuses seem to be rather the actions of one set upon mischief than distracted or lunatic.

Buckinghamshire

In 1696 a parish was ordered to pay £2 to the master of the house of correction

> for certain necessaries for keeping a lunatic that killed his wife and has few lucid intervalles.

North Riding

In 1633 a man was ordered to appear before the quarter-sessions to be bound over, but

> on appearing seemed to be a distressed and distracted person and not capable what he does or says.

Consequently, the parish officers were ordered

> to take him into their safe-keeping and look to him that he do no harm.

The information on the management of lunacy found in local historical documents is, on account of its nature, not only widely scattered, but also very fragmentary. It is impossible to reconstruct the whole course of events in even a single case of lunacy; it is not known how long the insane had to stay in the houses of correction nor how their lives ended. Nevertheless, this information is of interest. In these records lunacy and its economic consequences are seen from the point of view of the ordinary people and from that of the authorities. An investigation of these records helps one to understand why during the seventeenth century the general attitude towards the insane was bound to be hostile. The descriptions given leave no doubt that in many cases the presence of a lunatic person constituted a real danger to the whole parish. Moreover, since the passing of the Elizabethan Poor Law Statute, the maintenance of such a person had frequently become the responsibility of the parishes whose financial resources were often very limited. One has to add to these facts the general conviction that harsh treatment was not only necessary, but that it was even regarded as being beneficial in the management of the lunatics. The records also make it clear that the legislation on lunacy, passed during the eighteenth century, can be traced back to the methods employed by the Justices of the Peace during the preceding periods. The Statute 17 Geo. II. c. 5, which was passed in 1744, dealt, according to its title, with rogues, vagabonds, &c. Section 20 of this Act, however, was concerned with the management of lunacy, because lunatics were at this time still regarded as "disorderly persons". The Act gave the Justices the power to have dangerous lunatics "apprehended, and kept safely locked up in some secure Place and (if the Justices find it necessary) to be there chained". Further, it was laid down that either the parish or the relatives of the insane person were to be made responsible for "reasonable charges of removing and keeping, maintaining and curing such Persons during such Restraint". As had happened previously, the Act only made legal those methods which had been already found useful in practice for a long time. The origins of the private mad-houses which from the eighteenth century onwards played such a conspicuous and sad part in the management of the insane, can be found in the method used by the parish officers in the seventeenth century, when they had been ordered to take charge of a lunatic parishioner.

From about the third decade of the eighteenth century onwards, no more references to the management of lunacy can be found in the quarter-sessions records. Once the parishes had started to send all the persons who were in need of relief to the workhouses, there was very little opportunity left for the Justices to intervene in the administration of the relief of the poor. If they had to sign an order for the admission of a lunatic to the house of correction or to the workhouse, they did so "out of session", e.g. in their homes.

I wish to thank Mr. R. Sharp-France, Archivist of the Lancashire County Council, for having given me the facilities for the investigation of the Lancashire quarter-sessions records.

REFERENCES

BURTON, R. (1621) The Anatomy of Melancholy. London.
COKE, E. (1648) Institutes of the Laws of England. London.
DALTON, M. (1635) The Countrey Justice. 3rd Edn. London.
HALE, M. (1778) Historia Placitorum. Edited by S. Emlyn. London.
JONES, K. (1955) Lunacy, Law and Conscience, 1744–1845. London.
MCMENEMEY, W. H. (1955) *Proc. R. Soc. Med.*, **48**, 593.
TOLLIT, S. S. (1954) *Trans. hist. Soc. Lancs. Ches.*, **105**, 85.
WILLIS, Th. (1685) The London Practice of Physick. London.
The Constables' Accounts of the Manor of Manchester (1891) edited by J. J. Earwaker. Manchester.
Buckinghamshire Sessions Records (1930) edited by W. Le Hardy, and G. Reckitt. Aylesbury.
North Riding Sessions Records (1884) edited by J. C. Atkinson. London.
Somerset Sessions Records (1912) edited by E. H. Bates Harbin. London.
Warwickshire Sessions Records (1935) edited by H. S. Johnson and S. C. Ratcliff. Warwick.

A PAPER entitled **Sir John Pringle as Hygienist** was read by Mrs. DOROTHEA WALEY SINGER.

[*June* 6, 1956]

Miss Florence Nightingale and the Doctors

PRESIDENT'S ADDRESS

By Sir ZACHARY COPE, M.S., M.D., F.R.C.S.

MISS NIGHTINGALE once wrote "I can always talk better to a medical man than to anyone else". One is therefore encouraged to think that by a study of her relations with doctors it may be possible to get a truer picture of her character than by other lines of investigation. She had many medical interests and no woman in the Victorian era had so much influence on the improvement of the public health. At every stage of her public career she met doctors, and among them were some of her best friends. She was a convinced sanitarian; by her exposure of the bad sanitary conditions in barracks she undoubtedly led to great improvement in the health of our soldiers; and she virtually founded the Army Medical College. She made a brave attempt to classify diseases on a surer basis, and she just failed to institute a uniform system of hospital statistics. All these quite apart from her work on nursing.

We depend for our information chiefly on correspondence and memoranda, and it is only fair to state that in these we often get Miss Nightingale's first sharp reaction to events, a reaction which was often violent and uninhibited. When she came to write for publication, or when discussion with authorities became necessary, she was much more restrained and moderate, and measured her words carefully. Most of Miss Nightingale's work was done without publicity. No one so carefully concealed the part she played. Her seclusion was her defence and her invalidity protected her secrecy.

She was a merciless, but usually just, critic of the medical profession and of medical treatment, but she was in no doubt as to the great power which the united profession wielded. She warned Chadwick not to antagonize the doctors and she once stated that though in her book on nursing she had sailed as near the wind as she dared against them, she would have liked to go farther.

She would have made an excellent doctor herself. Here is her view on medical practice: "Medicine is a mere matter of experience of which we do not yet know the rules. If I were a doctor I never would argue with my patient, because then 'he' thinks his argument may be as good as mine. I would say 'this' is the matter, 'that' is what you are to do. If you don't do it, send me away."

A better summary of Miss Nightingale's method of dealing with people in general could not be found. At that time there was little scientific medicine, and her judgment that "there is no great use in physic either way" was, for that time, correct.

Of medical organizations she was very critical. At one time when rearrangement of the franchise was being discussed and Universities were given the vote she wrote: "I won't have the College of Physicians represented, nor the Apothecaries; What! Give the franchise to the greatest credulity in the world, to the blindest adherence to prejudice and predestination—to the most obstinate opposition to all fact and experience—don't give it to the physicians or I'll get up an examination and every one of them will be plucked."

Though well educated in the humanities Miss Nightingale had no training in scientific method apart from statistics, and she looked askance at the new science of bacteriology.

In 1866 she wrote: "See what harm the German pathologists have done us. There are no specific diseases; there are special disease conditions. It is that which is bringing the profession to grief, and will in time work a great reform—to wit, to make them make the public care for its own health and not rely on doctrine. It is a great thing for weak minds—the doctrine of contagion."

All through her working life Miss Nightingale knew how to manage doctors, either by unanswerable logic, or by persuasion, or by sheer cajolery, or by bullying, or, if need be, by intrigue. She was a master of intrigue, and on several occasions she herself mentions that word to denote her activities. When she was superintendent of nursing at the Harley Street hospital, she wished to get certain regulations passed through the medical and the Ladies' committees. She first brought them before the Ladies' Committee, leading them to assume that the doctors had agreed and got their approval, and then she put them before the medical committee, telling them (correctly) that the Ladies' Committee had already agreed to them. In the letter to her father in which she recounted this incident she said she had come off with flying colours though if anyone had suspected her intrigue she confessed it would have ruined her.

She was a great believer in the healing power of nature, and, though she went to Malvern to be under the care of Dr. Johnson for the water-cure, she was under no illusions as to the reason why cures were achieved. She recognized that there was hydropathic quackery just as there were other forms of quackery, but she stated that at Malvern the benefit came from the whole way of life and not from the specific water-cure. When Chadwick argued that Mr. Roebuck had greatly benefited by his visit to Malvern she pointed out that Mr. Roebuck benefited by his absence from Parliament and from late night hours, and by his adoption of proper diet, quiet life, exercise, fresh mountain air and different kinds of bathing. She was fifty years ahead of her time in advocating open-air treatment for early tuberculosis. Where could you find a better account than this, written in a letter to Chadwick: "In incipient tuberculosis the water-treatment, not as a charm (as English women take medicine) but as part of a treatment, I have seen to be effectual, the rest of the treatment being open-air during the greater part of the day (riding or otherwise according to the patient's strength) bedroom ventilation at night, diet founded upon improved digestion, the result of the open-air exercise—sometimes gentle gymnastics, mild cold-water sponging and little wet-sheet packing."

She distinguished clearly between the seriously ill and the neurotic for on one occasion she defined the water-cure as "a highly popular amusement amongst athletic invalids who have felt the tedium vitæ, and those indefinite diseases which a large income and unbounded leisure are so well calculated to produce".

Biochemistry was then in its infancy. She knew Bence-Jones and said he was the best "chemical doctor" in London, but she did not think very much of mere chemical doctors.

Miss Nightingale possessed an unusual power of influencing the minds of certain types of men by her intellectual brilliance, her clear logic, and her indomitable will. She recognized this power and on one occasion named nine men whose lives she considered she had greatly altered by her personal influence. Five of these nine were doctors. She attributed her power, not to sympathy, but to the fact that they "debated and settled measures together". Their communion was intellectual. She noted that the men she influenced were mostly elderly men. It may be that their experience enabled them to recognize her ability, her intensity of concentration, and her transparent idealism. The doctors she mentioned were Alexander, Farr, McNeill, Ranald Martin, and Sutherland. Dr. Sutherland was a distinguished sanitarian who in 1855, when he was 47, was sent out to investigate the sanitary condition of the hospitals at Scutari and in the Crimea. There he met Miss Nightingale. Mrs. Woodham-Smith, in her brilliant epigrammatic way, wrote "He met Miss Nightingale at Scutari, became her slave, and his career was at an end". This is true, but less than the whole truth. He taught her sanitary science. By him she was led to believe that most if not all zymotic diseases were due to defective drainage and bad ventilation, that there was no such thing as contagion and that quarantine was useless. He gave her the knowledge that inspired her great work for the improvement of the health of the Army. In return, when the war was over, she saw to it that he was put on the Royal Commission for enquiring into the Sanitary State of the Army, and, later, on to the Sub-Commission which ultimately became the Sanitary Committee. He retained the latter post till he was 80 years of age. But the most important post he filled was that of unofficial confidential adviser and secretary to Miss Nightingale. Though she had no official Governmental position, Miss Nightingale was in effect a minister without portfolio, and Sutherland was her principal private secretary. Cabinet ministers, Viceroys of India, and many medical and other professional men of high standing sought her opinion and often followed her advice. On every subject, before making her decision, she was accustomed to consult with Sutherland.

He was a man of sound common sense. He had not the burning enthusiasm nor the vivid

imagination of his colleague but he knew the best way to get things done and had a closer touch with reality. Between them they accomplished great things.

Though Sutherland received pay from the War Office for his official duties, Miss Nightingale gradually required more and more of his time and sometimes became annoyed if he were not at her beck and call, which in fact he generally was. Perusal of their correspondence shows that he advised her on all her projects—and gave her very good advice which she did not always relish. She was often sharp and sometimes angry with him; she called him a man without a soul, and in letters to others said that he was forgetful and dilatory. When he said he felt ill, she ridiculed the idea. Hardly anywhere or to anyone did she praise him. Yet he was very faithful to her, took her harshness in good part, calmed her impetuosity and corrected her mistakes. Their correspondence continued for thirty years, usually business-like, occasionally playful, sometimes anxious, and very rarely almost affectionate. They were like imperturbable brother and domineering sister. Yet both well knew that it was she who had the power. When the Finance department thought of achieving economy by dispensing with Sutherland's services it was Miss Nightingale who persuaded them to retain him in his position. She, however, fully realized her dependence upon his help. She was lost without him. That was why he kept his position on the Army Sanitary Committee until he was over 80; after he retired there was no one who could or did take his place.

When, in 1891, he was dying and apparently beyond any further exertion, his wife told him that there was a letter from Miss Nightingale. To her surprise he roused himself, read through the letter and said "Give her my love and blessing". They were almost his last words.

It is difficult to find anywhere a parallel to the close co-operation of these two devoted workers, who in all their public work acted as one person. In the Dictionary of National Biography Sutherland is credited with most of the work they did together, and Miss Nightingale's name is not even mentioned. She was content to be in the background, but she was the stimulating motive-power and to her must be attributed a great part of the success of their efforts. Miss Nightingale diverted rather than ended Dr. Sutherland's career.

The man whose career she undoubtedly ended was Dr. (later Sir) John Hall, the principal medical officer of the Crimean Army. He was an elderly and senior officer at the time that he was posted to the Crimea from India. He had nothing to do with the preliminary arrangements nor with the choice of sites for hospitals. He was in no way responsible for the administrative muddle which led to such confusion. He was, however, a stickler for regulations, and when emergencies arose he had little or no initiative, and did his duty strictly within those regulations. In November 1854 Miss Nightingale arrived at Scutari. Unused to the conditions of warfare she was immediately thrust into the midst of the sick and wounded at a time of crisis after Alma and Inkerman when, it is safe to say, under the best sanitary conditions there would have been a big mortality. She was shocked by the bad conditions and by the mortality. Though submissive to Army regulations and discipline in the wards, she immediately began to write home to the Minister of War, pointing out defects, revealing the mismanagement, and indirectly blaming the principal medical officer. Provided with funds, placed at her disposal free from regulations, she was able to correct some of the deficiencies. By private request to the Minister she even obtained the promotion of a medical officer who supported her efforts—of course without consulting the P.M.O. She was secure in her support by the Minister, and it would have been asking too much to expect Dr. Hall to welcome her. He was always courteous but not very co-operative. The crisis came when in March 1856 a General Order proclaimed Miss Nightingale as having full authority over all the nurses in the Crimea, and with it there was an implied censure of Dr. Hall. The final incident which led to this General Order was apparently a misunderstanding on Miss Nightingale's part, but the whole matter was in effect a conflict of wills and powers and on both counts Dr. Hall was beaten. He was, and felt, humiliated. He wrote a dignified letter to the War Office which ended—"having been censured by the Secretary of State on information which is not correct, I request that you will do me the honour to submit this my explanation which I trust will be satisfactory to His Lordship." To his wife he wrote—"I am quite prostrated" and finished his letter thus: "I was told when I declined to interfere that, right or wrong, Miss Nightingale's friends were powerful enough to carry her through. My reply was 'So much the greater pity'."

Miss Nightingale had not yet finished with Sir John. She pursued with dynamic energy her determination to reform the Army Medical Service, and was responsible for the appointment of the Royal Commission which dealt with this matter. She contrived that six out of the nine commissioners appointed sympathized with her views. She and Dr. Sutherland took the chief part in choosing who should be called upon to give evidence, and it was chiefly she who prepared the questions which should be asked. She wrote to Sir John McNeill asking for information about Sir John Hall which might be useful in conducting his examination, and she added—"I would only recall to your memory the long series of proofs—his incredible apathy—to my mind with the exception of G. the worst of the liars".

No one could accuse Miss Nightingale of impartiality. Her manifest animus appears to have made some impression upon the mild Sidney Herbert for, judging from something she wrote to Sir John McNeill, Herbert appears to have expostulated with her.

That is the only possible explanation for the following note written by her to McNeill. "I am quite as well aware as he (Sidney Herbert) can be that it is inexpedient and even unprincipled to go back now into past delinquencies. What is more I feel for him who was victimized by a system of which he could know nothing until the results appeared. It is easy for me to be wise after the fact, me, who saw the results." Her conscience was troubling her, but only for a moment. She went on: "But it would be untrue and unconscientious for me to give evidence upon an indifferent matter like that of hospital construction, leaving untouched the great matter which will affect the mortality of our sick and wounded more than any mere architecture could do."

Sir John appeared before a Commission whose members had little sympathy with him, and was asked questions which, most likely, had been suggested by his chief opponent. He was at a grave disadvantage. After he had given evidence Miss Nightingale wrote that his evidence "fell harmless. It broke down utterly from want of truthfulness and perpetual doubling". Miss Nightingale herself did not appear before the Commission but very carefully prepared her written evidence which at a later date she published separately. She was therefore not spontaneously questioned by the commissioners. There have been few cases in history in which public clamour and private intrigue have combined so completely to make a case against a man who, as his chief opponent confessed, was the victim of a system for which he was not himself responsible.

Miss Nightingale knew that her Army reforms were not likely to be implemented if Sir John Hall were to be appointed Director-General, as appeared at one time likely. She therefore successively and successfully approached Lord Panmure, and, through Sidney Herbert, General Peel, and obtained their promises that Hall should not be appointed Director-General. She then pressed the nomination of Dr. Alexander upon Sidney Herbert, and it was Alexander who was appointed D.G. on the retirement of Sir Andrew Smith in 1858. This was, undoubtedly, a good appointment. Sir John Hall, a broken man, retired on half-pay and died abroad in 1866.

There was another Sir John whom Miss Nightingale first met during her war service in the East—Sir John McNeill—whom she greatly admired and whose advice she often sought and, what is more wonderful, frequently followed. McNeill was a graduate of Edinburgh who entered the service of the East India Company as an assistant surgeon when he was only 23 years of age. He was sent up to Persia where his ability was such that he was appointed Assistant Chargé d'Affaires. His distinguished diplomatic service was rewarded by a G.C.B. in 1847.

When he retired he took up an official post in Scotland. The failure of the commissariat in the Crimea called for enquiry and Sir John McNeill and Colonel Tulloch were deputed to go out and make investigations. Their report was presented to Parliament early in 1856 and was welcomed by the public and the Press as a plain and reasonable explanation of the mismanagement, but Queen Victoria thought that it had been unwise to make public the report before those officers who had been mentioned in the report had had an opportunity of defending themselves. A military board was held at Chelsea and reported that the officers mentioned were not responsible for the muddle, and by implication McNeill and Tulloch were almost blamed for their report.

Public indignation, considerably fomented by Miss Nightingale and her friends, forced Parliament to correct this impression, and it was Sidney Herbert's speech in the House of Commons which led to their being publicly thanked, and to the bestowal of a knighthood on Tulloch and a Privy Councillorship on McNeill.

When the scheme for reform of the Army Medical Service was being prepared it was Sir John McNeill who furnished Miss Nightingale with a detailed scheme for rearranging the administration—a scheme which she adopted with little alteration. Again when the Training School for nurses was founded, he was asked to serve on the first Council of the School. He was almost like a second father to Miss Nightingale and he kept up his correspondence with her nearly to the end of his life. He died in 1883 at the age of 88. In one of his letters to her he wrote: "You have a strength and a power for good to which I never could pretend.—You are leaving your impress on the age in which you live, and the print of your foot will be traced by generations yet unborn."

Almost as soon as she arrived at Scutari Miss Nightingale began to interest herself in the welfare and education of the young assistant surgeons in the Army. Within three months she wrote home to Sidney Herbert suggesting the formation of a medical school on the spot, and she offered to pay out of her own purse enough to fit up suitable accommodation for the purpose. On her return home she kept this aim in view and one of the results of the Commission of 1857 was the foundation of the Army Medical School or College. Dr.

Sutherland favoured a less ambitious plan but Miss Nightingale succeeded in getting what she thought was required. Colonel Lefroy drew up a draft scheme but Miss Nightingale amended it considerably. The draft had suggested that the School should be near London on account of the medical museums and libraries. Miss Nightingale wisely pointed out that the chief medical libraries in London were close boroughs. In the draft-scheme it was recommended that the would-be army surgeon should first go to a regiment for a year to be "broken in", and then go to the School for medical instruction. Miss Nightingale asked "What do the details of being broken in consist of? The more they are of medical men, the less of officers and mess-table men, the better. Go to School before you go to duty". It was she who insisted that the School should be directly under the control of the Secretary of State rather than the Director-General; most forward-looking of all, it was she who commented: "A most important part of this School would be to give medical officers from the Colonies, to whom periodical leave should be granted specially for the purpose, an opportunity of renewing their knowledge and practice and bringing it up to the level which civil medical science raises higher every year."

The School started at Fort Pitt, Chatham, and Miss Nightingale had the chief say in the nomination of three of the four professors. All three were good choices—Parkes, Aitken and Longmore. They had all seen active service in the Crimean War and two of them—Parkes and Aitken, had probably met Miss Nightingale at Scutari.

Edmund Alexander Parkes was a distinguished sanitarian, scientist and clinician, and, more than this, he possessed a noble character which did not fail to leave its mark upon the students he taught. He, more than anyone else, helped to weld the school together during the early difficult days. Miss Nightingale had the highest opinion of him and his work. On his deathbed he dictated a letter thanking her for all the support she had given him; she, on her side, in a letter to Sir Henry Acland wrote of him thus—"I think I have never known such disinterestedness, such self-abnegation, such forgetfulness of self".

Thomas Longmore, the professor of surgery, had served with the Light Brigade in the Crimea, with Alexander as his superior officer. While there he had been bold enough to write home to the newspapers making known the bad conditions under which the men were serving. That would certainly be a point in his favour with Miss Nightingale. She sanctioned his appointment on the recommendation of Alexander. She did not interview him before appointment. In 1864 Longmore wished to see her about some matter and she wrote to him—"I should be sorry to go out of this world without seeing the friend of my dear friend Mr. Alexander". She had waited four years to see him and she granted him exactly a quarter of an hour.

Longmore was quite a success as a lecturer and wrote some useful articles on various surgical subjects. He acted as British representative at several conferences which discussed the new Red Cross movement and the Geneva Convention. Miss Nightingale did not think much would come from the movement, but agreed that it was on the right lines. She wrote: "I agree with you it will be harmless for our Government to sign the Convention as it now stands. It amounts to nothing more than a declaration that humanity to the wounded is a good thing. But it is like vows. People who keep a vow would do the same without a vow. And if people will not do it without a vow, they will not do it with."

Longmore was knighted in 1887. He retired from the professorship after twenty-five years' service and died in 1895. Rather late in life he wrote an excellent life of Richard Wiseman.

Dr. William Aitken was appointed professor of pathology in the Army Medical School. He was an Edinburgh graduate who had become pathologist to the Royal Infirmary, Glasgow, and, in 1855, had gone out with Dr. Lyons to investigate the diseases afflicting the troops in the Crimea. There he must have met Miss Nightingale and it may have been from him that she derived her undoubted interest in pathology. Aitken had the unenviable task of building up a department under a War Office which delayed supplies and material, and needed constant prodding. He wrote many letters of complaint to Miss Nightingale and she in her turn agitated till things were done. The department was not in anything like order when the students arrived, but ultimately it was equipped. Aitken was not only a pathologist; he was a good physician and wrote a two-volume textbook of medicine which went through several editions. He was elected a Fellow of the Royal Society and in 1887 was knighted. He remained in his post as professor at Netley until 1892 when he retired; he died three months after his retirement.

With the Directors-General of the Army Medical Department Miss Nightingale was sometimes friendly, sometimes not so friendly, according to their attitude towards reform, and more particularly *her* views on reform. She had a poor opinion of Sir Andrew Smith who was D.G. during the Crimean War, and she altogether disapproved of the method whereby promotion was left to his discretion. After he had given his evidence before the Royal Commission she commented: "Did not Sir A. Smith's evidence yesterday amount to

this? I act upon no rule. I have neither selection nor seniority.—I have under me, gentlemen, educated men who are like beggars without any knowledge of what tomorrow's prospects are. They have no rule to depend upon but my judgment of what is best for the service. This is the system of Army Medical Government and I consider it a perfect one, perfectly administered." Miss Nightingale for doctors preferred promotion by examination. When Sir Andrew retired in 1858 it was owing to her representations that Dr. Thomas Alexander was appointed D.G. Alexander was one of the few senior officers serving in the Crimea who both criticized and tried to remedy some of the distressing failures of administration. Dr. Sutherland noted his ability and urged his being made a member of the Royal Commission of 1857. When he was appointed D.G. in 1858 he at once began to implement some of the changes which had been recommended. Within six months a Royal Warrant was issued giving improved pay and relative rank to Army Medical Officers, and the service was generally improved. But he appointed two members to the Advisory Board without consulting Sidney Herbert or Miss Nightingale, and this brought down her wrath upon his head. Miss Nightingale wrote: "Alexander goes and surreptitiously recommends two of his own creatures to General Peel—so that the Board is nothing now but one more of the hugger mugger boards of Andrew Smith's plus Balfour.—I hear Alexander is heartily ashamed of himself." And so forth.

Before Alexander could carry out all the reforms which he undoubtedly would have done, he was taken ill and died. He was succeeded by Dr. James Brown Gibson who did not please Miss Nightingale. In 1864 she wrote to Sir James Clark saying she was "intriguing" to get Dr. Muir in Gibson's place. She did not succeed. Gibson retired in 1867 and was succeeded by Galbraith Logan who does not appear to have had correspondence with Miss Nightingale. He was succeeded by Dr. Muir who had quite an amicable correspondence with her.

Miss Nightingale was disappointed with the development of the School but in 1882 Sir Thomas Crawford became D.G. and he became her close friend and supporter. She corresponded with him about the nursing in the Army and drew up a scheme for a regular nursing service. Later she honoured him with the highest mark of her esteem by asking him to serve on the Council of the Nightingale Training School for nurses. He died in 1895.

Miss Nightingale avidly absorbed facts and feasted on figures. From her youth upwards she had an aptitude for mathematics and she never tired of accumulating data and calculating percentages. She had a great liking for Blue books. At that time Dr. William Farr was the best-known medical statistician. His name was given her as that of one who was likely to be of help to her. She tried to get him as a member of the Royal Commission of 1856–7 but he was only made a member of the Statistical Sub-Commission. A great friendship grew up between Dr. Farr and Miss Nightingale, and there ensued a long correspondence which dealt with many matters other than statistics. Dr. Farr called her one of his "aptest workmen", and he nominated her for the membership of the Statistical Society. On her side she tried to get him elected a member of the French Institute; she did succeed in getting him made a corresponding member of the Institute, but it was Gladstone who was chosen for the vacant membership. They worked together on many subjects. He was full of admiration for her statistical diagrams which gave at a glance the percentage mortality of the soldiers in the Crimea. "This speech is the best that was ever written on diagrams or on the Army.—It is the perfection of writing with diagrams and tables before you, to render unnecessary any reference to them. This you have done." They collaborated on statistical tables of mortality in different hospitals, and in the special case of mortality following operations. Miss Nightingale tried to obtain figures which would enable her to compare the efficiency of one hospital with that of another—a rather invidious task. Farr wrote for the *Lancet* and Miss Nightingale made use of this for purposes of propaganda. When Sidney Herbert was expecting opposition in the House of Commons to the expense of the Army Medical School, she wrote a note on the subject, sent it to Farr, who added a sentence or two and then sent it on to the *Lancet* for publication. Thus, as was intended, Mr. Herbert was able to quote a civilian medical journal in favour of his scheme. Clever beneficent intrigue. Miss Nightingale contributed statistical papers to the Social Science Congress at Liverpool in 1860 and to the International Statistical Congress at Berlin in 1863. Her papers were read by Farr or some other friend. She became acquainted with the well-known statistician Quetelet, and when in 1874 he died she wrote of him and the science he represented in a letter to Farr: "I cannot say how the death of our old friend touches me; the founder of the most important science in the whole world; for upon it depends the practical application of every other and of every art; the one science essential to all political and social administration, all education and organization based on experience, for it only gives exact results of our experience."

Farr was not well off and when he retired a subscription list was opened to help him. Miss Nightingale subscribed ten guineas, but after his death she sent an additional hundred pounds.

One of Miss Nightingale's friendships had, indirectly, an important influence upon the

development of the nursing profession. When she returned from the Crimea, her chief interest was Army Medical reform. She was in no hurry to found a nurses' training school. It was her friends—Sir John McNeill, Dr. Farr and Dr. Sutherland—who kept urging her not to delay in founding such a school. Not till 1860 was the school opened. In connexion with this school there were two peculiarities which gave rise to difficulties. Miss Nightingale held the view that no examination could give a true picture of the suitability of a nurse, for it left out the question of her character; and she was strongly opposed to giving any nurse a certificate of qualification, even though she had been an exemplary student and had given every satisfaction. Whether right or wrong, this made it impossible to set a general standard of nursing which could be measured by any easy method of comparison.

Dr. (afterwards Sir Henry) Acland attended professionally some of Miss Nightingale's relatives and he was a friend of the family. He was one of the original members of the General Medical Council, and, in 1872, he had a firm conviction that there should be better regulations for the education of women, particularly for those occupations allied to medicine. At his suggestion a committee of the General Council was set up—with himself as chairman—to investigate "what are the most desirable means for educating, examining, and certifying in respect of them (i.e. qualifications for women) with special reference to midwifery, the management of medical institutions, dispensing and nursing". Dr. Acland promptly wrote to consult Miss Nightingale about the matter, but she poured cold water on the project. The committee went on with their work, however, and in March 1873 Acland wrote again, this time sending the draft report of the committee and asking for criticisms. He had left her little time but she quickly got to work and sent her reply by special messenger. She was opposed to the scheme. She thought there was perhaps a case for certifying midwives, but not for certifying superintendents of institutions (matrons) and nurses. She told Acland plainly that he had not enough information to justify action, and said all he could do was to get the committee reappointed to continue their investigations. Her advice did not change his opinion but it stopped his action. He showed her the final revision of the report and agreed not to make any recommendation except for the reappointment of the committee. The next year he was made President of the Council but the matter of the registration of nurses was not again brought up. There is little doubt that, but for Miss Nightingale's strongly-worded protest, there would have been some standardization of nursing, some form of examination and certification, a generation earlier than actually occurred. It may well be that matters were not then ripe for any regular registration of nurses, but Sir Henry, who had a wide knowledge of methods of education, thought that legal recognition should be accorded to them as early as 1872.

Miss Nightingale had many other medical friends. Her favourite surgeon was Sir James Paget, of whom she spoke with admiration and almost affection. He was the first to give her active help in her scheme for obtaining more accurate hospital statistics. At St. Bartholomew's Hospital a registrar was appointed and accurate statistics were obtained and published. Paget was delighted with Miss Nightingale's "Notes on Nursing" and declared that he had learnt a lot from reading it. When he was made one of the Trustees for the Women's National Jubilee Fund he consulted her over the scheme for the Queen's Institute. She was also pleased with the impartiality he displayed over the vexed question of the registration of nurses, though, in reading about this, one gets the impression that Sir James' good nature may have prevented his saying all that he might have said. In this, as in so many instances, we have only the one side of the question presented to us.

Miss Nightingale did not know Sir William Savory personally, but that did not prevent her writing him a long screed setting out her views on the registration of nurses, in an effort to persuade him not to continue his support of that movement.

Sir James Clark, the well-known physician to Queen Victoria, was a good friend to Miss Nightingale for many years. He it was who, by his personal advice to various members of the Nightingale family, encouraged Florence to break away from the thraldom of her mother and sister. It was he who gave her a personal introduction to Queen Victoria. She in her turn strove hard and successfully to have him appointed one of the Commissioners in 1857, and she appointed him a member of the Council of the Nightingale Fund. He continued to give her his active support till his death in 1870.

Other influential friends were Sir William Bowman, the distinguished ophthalmic surgeon, Dr. Bence-Jones the well-known physician, Dr. Pattison Walker, at one time professor of hygiene at Calcutta, and Elizabeth Blackwell, the first woman to be put on the medical register of this country.

No account of Miss Nightingale and the doctors would be complete without a reference to her own medical attendants, and a short discussion of the nature of her invalidity. She had little or no faith in the usual medical remedies. Her medical friends, when they saw her overworking, advised her to rest, but she flouted their advice. At different times she consulted Sir James Clark, Sir John McNeill, Dr. Sutherland and a certain Dr. Phillips, but she was a law unto herself. The treatment which she thought saved her life at Malvern was the

water-cure, but she knew that the benefit was largely due to the manner of life there. In her old age she was under the care of Dr. May Thorne.

Why did Miss Nightingale become an invalid? Why did she spend more than half her long life cooped up in one room, eating her meals alone and only seeing visitors, whether relatives, friends or those wishing to consult her, by special appointment? Why did she complain of such continuous pain and speak of herself as a weak person who could make no exertion, when we know she got through more work than two average active persons? She was not paralysed; she certainly had no serious organic disease; she lived to a ripe old age and saw most of her younger friends die before her. The answer to these questions can only be given if we study the history of her case.

Florence Nightingale was the younger of two sisters. Her mother and elder sister were strong-minded and fond of social life into which they tried to draw Florence. But Florence was thoughtful, introspective and filled with an eager desire to do something useful in life. At the age of 17 she had a mystical experience which she took to be a call from God. When 24, she felt she had a vocation for nursing but her family were horrified at the idea. She heard of the Deaconess Institute at Kaiserswerth and determined to go there for training. In 1851 in spite of her family's opposition she spent three months there. Her sister accompanied her to the door. As she was going in she offered her bracelets to her sister who, in a fit of rage, threw them back in Florence's face. Florence fainted and later wrote down that that was the first beginning of her grave illness. After her return from Kaiserswerth her sister and mother again tried to domineer over her, but this time they failed, for she was beginning to find her mental freedom. Her mental frustration was intensified by her definite refusal to accept the proposal of marriage from Richard Moncton Milnes (afterwards Lord Houghton), because she thought he would not fully sympathize with her moral aims in life. This repression of the sex-instinct was deliberate but took toll of her nervous system.

She seemed happier when she took the post as superintendent of nursing at the Harley Street hospital; she must have recognized her own great powers of administration, which were so soon to be used to the greatest extent in the Crimean campaign. During her two years abroad she worked to the extreme human limit of both mind and body and she returned home a physical wreck—pale, thin, quiet, but determined to go ahead with the project of reform of the Army Medical Service. For another year she worked as one possessed. Her continued energy frightened her friends but she would not lessen her efforts until in August 1857 she and Dr. Sutherland finished the report of the Commission. Then she collapsed utterly. Her pulse-rate was rapid and at Malvern her doctor told her she must lie down until the pulse became normal. From that time to the end of her life she spent most of her time in bed or on a couch.

We see then that for almost ten years she had lived a life of great emotional conflict and frustration. On top of this, with great difficulty, as evidenced by agonized entries in her diary, she had refused marriage with a man she loved, and on top of that she became physically and mentally fatigued to the point of exhaustion. No one could live through such experiences without some nervous reaction and there is no doubt that Miss Nightingale's invalidity was a neurosis. For some time any extra exertion, any unexpected hindrance or annoying opposition, any unpleasant visitor, was likely to induce palpitations, rapid breathing, perhaps faintness, and complaint of pain. Like so many neurotics Miss Nightingale after a time frequently referred to the severe pain she suffered, while pooh-poohing the pains and complaints of others. In spite of all her complaints she was always able to work at anything which interested her.

Why did she not recover? As matters became more easy why did she not become more socially active? Well, what inducement was there for her to recover? She cared nothing for the usual social activities and she found that any person she wished to see, however distinguished, would come to see her at her convenience. Moreover it is, I think, undeniable that her invalidity protected her from the active opposition of some who did not agree with her views. They refrained from saying, writing, or doing anything which might hurt an invalid's feelings. Though I am far from saying that Miss Nightingale purposely exploited her invalidity there is little doubt that in some ways it was an advantage to her in her work. She could think without interruption and write to her heart's content. And she had a most able and devoted doctor colleague who did all the work which demanded visits to be made or work to be done outside. There is a close parallel between her and Miss Barrett the poetess. You will remember that Miss Barrett's invalidity quickly got better when Robert Browning appeared; but Miss Nightingale had deliberately and decisively sacrificed marriage to her mission in life. And who shall blame her?

[I wish to acknowledge my indebtedness to the Commandant of the Royal Army Medical College, and to the authorities of the British Museum and the Bodleian Libraries for allowing me access to documents in their keeping, and to the executors of Miss Nightingale for permission to publish extracts from them.]

Section of General Practice

President—GEOFFREY BARBER, O.B.E., M.A., M.B.

[*March* 21, 1956]

Cord Round the Neck

By C. W. WALKER, M.B.

FOR over 200 years (Chapman, 1753; Denman, 1816; Roques *et al.*, 1955) midwives have been taught that when the head is born in a vertex presentation, they should feel for the cord round the neck, and, if found, loop it over the head, slip it over the shoulder or divide it. The reasons for this instruction are stated to be that the tight cord will asphyxiate the child or that it may cause delay in delivery, separation of the placenta or rupture. This reasoning is wrong. If the child is alive when the head is born, the rest of the body may be delivered without dangerous tension on the cord because of the descent of the fundus during delivery from near the xiphisternum almost to the symphysis pubis. It may be necessary to assist this descent by fundal pressure during a contraction.

While cord round the neck in a vertex has attained undue prominence in the textbooks, cord round the neck as an important cause of breech presentation has been ignored. Yet if the head and neck are tethered to the placenta which is normally in the fundus, the breech will present. This cause of breech presentation is of added importance nowadays when in antenatal clinics all over the country breeches are being turned by external cephalic version. When the cord is round the neck, version may kill the child by constricting the placental blood supply.

Fig. 1 shows the cord round the trunk, round an arm and round the neck and the placenta near the fundus. There is also a knot in the cord. Version on such an infant would damage the child and probably the mother as well.

FIG. 1.—". . . and the funis with a knot upon it surrounds the neck, arm and body."

Reproduction of engraving of a breech presentation taken from Thomas Denman's "Introduction to the Practice of Midwifery", 1816.

In Table I are listed the presentations during labour of 574 cases from my records. Cæsarean sections are included.

Table II gives the infant mortality when the breech presented, both for those which were

TABLE I

Vertex—unmanipulated including 3 Cæsarean	519
Vertex—successful external cephalic version ..	31
Breech—including 2 Cæsarean	24
	574

TABLE II.—INFANT MORTALITY AFTER BREECH PRESENTATION

No.	Treatment	Mortality
31	External version..	1 erythroblastosis
24	Breech labours, failed version and no version	4
55		5

TABLE III.—ANALYSIS OF BREECH LABOURS

Cause	Cases	Mortality
Cord round neck (Cæsarean)	5	1
Extended legs and probable cord round neck	1	
Cord round thigh	1	1
Twins	2	
Placenta prævia	1	1
Contracted pelvis	1	1
Extended legs	7	
No cause found, incl. 1 Cæs. for toxæmia	6	
Total	24	4

successfully turned and for those which went into labour as breeches. One infant was stillborn due to erythroblastosis after successful version.

In Table III an attempt is made to determine the causes of breech presentations. In 5 deliveries the cord was found round the neck and this was considered to be the cause of the presentations. A sixth had been diagnosed as cord round the neck but there is no note (hospital delivery) about the position of the cord.

Case summaries of the 5 infants born with cord round the neck.

(1) 2 para. Attempts at version at 38/52 caused fœtal distress. Precipitate labour. Midwife arrived twenty minutes after delivery and found child born except for face and head which were just inside vulva. Cord round the neck had prevented complete spontaneous delivery and caused death of the child from asphyxia.

(2) 3 para. After 3 easy external versions during pregnancy, a breech again presented at 41/52. Attempt at version caused fœtal distress. Diagnosed as cord round the neck of a large baby. Delivered in hospital by Cæsarean section. Living child, 10 lb.; cord twice round neck.

(3) Primip. Attempt at version failed at 36/52. Breech delivery at full term. One arm extended, cord 4 times round neck.

(4) Primip. Attempt at version failed at 35/52 and 37/52. Uncomplicated breech delivery at 38/52. Cord 3 times round neck.

(5) 2 para. Attempt at version failed at 35/52. X-ray showed breech with extended legs. Spontaneous breech delivery at 38/52 with cord round neck.

Case summary of infant with cord round thigh.

2nd para. Version in hospital at 32/52. Complained to me that she had felt no movement since child was turned. Examined 33/52 L.S.A. Confirmed by X-ray—no sign of fœtal life. At 35/52 delivered in hospital of a stillborn macerated breech, cord being tightly wound round (R) thigh and (L) leg.

Why version from breech to vertex should cause tension on the cord and death of the infant requires an explanation. It is suggested that turning the head towards the feet might have tightened the cord if this could not slip over the shoulder. Alternatively, a mistaken diagnosis might have led the obstetrician to do an external podalic version and so caused tension on the cord.

Conclusion.—The figures given are not statistically significant, but they would seem to indicate that cord round the neck is at least as important as placenta prævia, contracted pelvis or multiple pregnancy in causing the breech to present. Just as the practitioner is expected to diagnose these other causes, so he should be aware of the possibility of cord round the neck. If attempts at version cause fœtal distress, he should desist from his efforts and decide whether to manage a breech labour or ask for a Cæsarean section.

The growing practice of external version will fail to achieve its object—which is the removal of the 10% fœtal mortality of breech deliveries—if a substantial proportion of infants are killed by version.

Summary.—Cord round the neck of the fœtus *in utero*, while seldom harmful in a vertex, is an important cause of breech presentation. Some figures are given in support of this statement which has a bearing on the growing practice of external cephalic version in ante-natal clinics.

In replying to the discussion, Dr. Walker suggested that the following precautions might be taken by the practitioner dealing with a breech:

(1) The diagnosis should be confirmed by X-ray.

(2) No anæsthetic should be used for the version.

(3) The fœtal heart should be counted before and after, and, if there were difficulty, during the version. Fœtal distress indicated by exaggerated fœtal movements or slowing of the heart for more than a few seconds would be a sign that manipulations should stop.

(4) If the presentation repeatedly reverts to a breech after versions, however easy, special care should be taken as the risk of tension on the cord increases as the child grows larger.

REFERENCES

CHAPMAN, E. (1753) Improvement of Midwifery. London, p. 126.
DENMAN, T. (1816) Introduction to the Practice of Midwifery. London. p. 330.
ROQUES, F. W., *et al.* (1955) Midwifery by Ten Teachers. London. p. 128.

The Care and Treatment of Acne Vulgaris

By Sir Walter Fergusson Hannay, M.R.C.S., L.R.C.P.

We have all seen the deep pitting and scarring of the face and back resultant on neglect of treatment. Early and vigorous treatment of acne can save many patients from a lasting disfigurement of face and of mind.

Acne vulgaris is a chronic inflammatory disease of the pilo-sebaceous gland system of the skin. It appears at puberty and increases during adolescence. The acne bacillus and the staphylococcus are associated with this condition and, though present on normal skins, the acne patient appears to have lost his immunity to these organisms.

In puberty the outer covering or envelope of the body becomes thicker and coarser. There is an increase in the thickness of the corneal layer of the skin with involvement of the orifices of the pilo-sebaceous follicles. Hypertrophy of these follicles leads to an increase of sebaceous secretion. This metamorphosis results in a varying degree of seborrhœa. The skin becomes greasy and the hair follicles hypertrophy and become filled with sebaceous secretion and debris. In the scalp this secretion is known as dandruff.

Girls as well as boys may suffer serious disfigurement from the ravages of acne. It is not necessary, in this psychologically conscious age in which we doctors practise our art to-day, for me to stress the severe psychic trauma young persons may suffer when they discover that their bodies, and especially their faces, are being disfigured and discoloured by pimples, pustules and blackheads.

Many General Practitioners discourage young patients when presenting themselves on account of their spots and make light of their disfigurement. These sufferers are too often told that nothing can be done for their complaint, and that in any case they will grow out of their pimples. The mental distress these unfortunate patients suffer is not appreciated, and the resultant scarring—sequelæ of neglect of treatment—that these sufferers will carry with them to the grave, forgotten.

When a patient first consults me I explain the importance of carrying out conscientiously the treatment. I outline the nature of the skin changes which are taking place, and briefly survey the results of the chemical activity of the body upon the skin. Such a talk is greatly appreciated by the patient and has a most beneficial psychological effect.

The importance of diet in this disease is impressed upon them, and a low fat, low carbohydrate intake is advised. Sweets and especially chocolates are a constant cause of spots. Buns, pastries and the stodgy foods all tend to an excess of seborrhœa. A diet of fresh fruit and vegetables with a high protein intake and plenty of fresh water is advocated. Alcohol, though fortunately not usually a problem of the young, is also to be avoided. Many doctors rightly fear the effect of dieting the young, and, with this in mind, I add vitamins to the diet. Because dermatologists hold varying opinions on the importance of diet in acne, and many patients do not care to forgo the delights of chocolates, I ask my patients to adhere strictly to my diet for six weeks, and then return to their old eating habits. Nearly all patients find an exacerbation of their acne on their normal diet, and willingly resume the prescribed regime.

Constipation is always present in acne cases, associated with liver stasis and small intestine toxæmia, with a constant presenting symptom of halitosis. I therefore prescribe for all these patients magnesium sulphate in the form of mist. alba to be *taken at night*, when it acts more readily on the liver and upper bowel, and is not purgative as when taken in the morning. The patient varies the dose to avoid passing a loose stool.

Hormone therapy must be undertaken with great care. In men with severe pustules and scarring, stilbœstrol 5 mg. daily is most effective, but must be given in very short courses, as the breasts may hypertrophy and there may be a depressing effect on the testes. This effect is not permanent and is reversible. For this reason stilbœstrol should never be given to youths under the age of 18. In girls suffering from aggravation of their spots at the time of the menses, and often with irregularity of the periods, I prescribe dienœstrol in doses varying from 0·3 mg. to 1 mg. daily to be taken fourteen or twenty-one days after the first day of the last period and continued up to the onset of the next period.

In treating the skin lesions, I aim at reducing the effects of excessive seborrhœa, sterilizing the skin surface and removing the comedones. Personally, I discourage the scrubbing of or even washing the face and back with soap and water, on the principle that oil and water do not readily mix, and, when they do, they form an emulsion which is harmful to the skin. The face and affected skin surface should be cleansed with a cationic detergent, such as cetrimidum (C.T.A.B.) 1%. Many patients also find that the top of the milk is a powerful cleanser and grease remover.

Potassium permanganate in weak solution is a useful disinfectant, when added to the bath. For dandruff the scalp should be massaged daily with a lotion containing hydrarg. perchlor. and acid salicyl. and weekly shampoos with either 10% C.T.A.B., ether soap

or Sebbix. Blackheads must be removed with a comedone extractor, and pustules lanced with a sharp sterile needle. Pustules and infected cysts should never be lanced with a scalpel, as this always leads to linear scarring. On no account should pimples or pustules be squeezed, as this damages and reinfects the surrounding tissues. Lotions and ointments containing sulphur, resorcin and other rubefacients are disinfectant and improve the capillary vascular supply by producing a mild hyperæmia and exfoliation of the skin. Calamine is soothing to the skin and useful to produce skin-tinted ointments. It may be necessary to ring the changes with local applications to obtain the best cosmetic effects.

In severe cases and especially in the presence of gross scarring the application of CO_2 slush gives remarkable results. CO_2 snow is converted into a slush by adding acetone, and the resultant slush is then painted on to the affected areas with a camel-hair brush. Great care must be taken to cover the eyes when working on the face. Ultraviolet light, when natural sunlight is not available, will frequently clear the face and back of acne. X-ray therapy has a place in the treatment, but should only be given by an expert. In recommending any form of physiotherapy, it should always be remembered that this can be very time-consuming.

Vitamin A in large doses, 24,000 to 50,000 units daily, has been found to reduce the eruption of pustules, and is especially satisfactory in cases with infected cysts and nodules. In very resistant cases a course of anti-acne and staphylococcus vaccine may turn the tide. The sulphanilamides may be necessary in severe pustular forms.

The skin must be cleansed with 1% C.T.A.B. and the affected parts treated with Lotio Alba every evening. In the daytime a cream such as

Resorcin	.. 2%	or	Resorcin	.. 2%
Sulphur	.. 8%		Sulphur	.. 8%
Alcohol	.. 10%		Alcohol	.. 10%
Adeps lanae	5%		Glycerin	.. 5%
L.E.B.	ad 100%		L.E.B.	ad 100%

can be applied as a face mask. The base used in this cream will depend on the ability of the particular skin to absorb the ointment.

I should like to take this opportunity of thanking Dr. G. B. Mitchell-Heggs for his kind permission to treat the cases under his care at St. Mary's Hospital.

The Importance and Proportion of Minor Ailments in General Practice

By Bertha Turner, M.D., B.S.

I have in mind especially an enquiry into the number of cases, if any, of serious conditions which may come to light after a period of attendance for apparently minor complaints. Or, more precisely, is the constant attention which we all give to Minor Ailments largely preventive, or curative in itself?

The minor ailment is a definite entity. It is essentially a condition of Dis-Ease. It is often relieved in the early stages; firstly by full examination, and any therapeutic treatment indicated. Then, often, by discussion, involving a good deal of listening.

I exclude the minor ills of accidental origin; early sepsis and infections; also definite signs and symptoms of organic trouble relating to respiratory, cardiovascular, digestive, or any other system, in early stages.

We are left with a host of indefinite complaints which the patient relates to something wrong, and which is causing distress, anxiety, and inefficiency in work. For example, headache in various forms, but from no apparent cause. Indigestion which has so often to be proved to be of non-organic origin before it can be cured. Insomnia, or poor quality sleep. Minor degrees of fleeting and shifting muscular rheumatism, likewise varying degrees of catarrh and other allergic states. Dysmenorrhœa and menopausal discomforts which may yield quickly to simple measures.

The common denominator in a large majority is that of stress and strain, and so often fatigue, although this is unrecognized by the patient. And this is why it is so rewarding to spend time and thought from the beginning. One can so often give them some insight into their physical and physiological needs.

I do not label these cases as functional. These complaints all have a physical manifestation, and are very real to the patient, yet they often lead us as family doctors into the fascinating paths of simple psychology.

When I take new patients on to my National Health Service list, I find it an asset to be able to invite them to come as often as they wish, and to bring any trouble, however small; explaining that it is to our mutual advantage to "keep them well", rather than to

"get them well" from a neglected complaint. It has been interesting to note the response to this open invitation.

It often turns out that the people who say they "never trouble the doctor" are just those who turn up regularly as soon as they have joined for one small complaint after another, and one begins to wonder whether they feel so well as they thought they did! But sooner or later they cease to attend. But the plan has worked, for when they come back some long time after, they may say that they have never felt so well. We seem to have cleared the ground.

I come now to discuss the proportion of my patients who attend for these minor ailments only. I refer to the proportion of persons on the files, and not to the proportion of attendances.

I have analysed a few groups for comparison:

(1) A group of small-fee surgery patients in a poor working-class district before the days of N.H.S. The 2s. 6d. or 3s. 6d. surgery fee of those days was hard to come by, and these were mostly women occupied with home cares, with their own complaints well in the background. 25% only attended for minor ailments.

(2) A mixed group in the current N.H.S. file. Chiefly professional workers, more women than men. Some children, and of course my share of the elderly and aged. 40%.

(3) An age group of University and Training-College Students, also N.H.S. These being subject to the special stress of the short period of concentrated work, with examination anxiety. They are an essentially healthy group. The infectious fevers, acute appendicitis, and other acute states occur from time to time, but an unexpectedly frequent cause for attendance is the minor ailment. 50%.

I said at the beginning that in no case could I find an example of minor ailments resolving into more serious states. The acute and infective conditions, the organic diseases, even at the onset, seem to present a different picture which puts one on one's guard. The complaint is more definite and seems to be in a category apart. Granted, of course, that the minor ailment patient such as I have been considering may develop a serious condition like anyone else; one has to be on the watch for the "old patient with the new disease" as Dr. J. D. Simpson so forcibly reminded us here a few years ago (1953, *Proceedings*, **46**, 353).

In conclusion I will mention two practical issues:

The first is the importance of having open hours in general practice, especially N.H.S. practice, with, of course, appointments as required; although I think the present trend is for appointments only. One can in this way see people who would not bother to make appointments, or who might think their complaint not worth this trouble. To walk through the open door without pre-arrangement is easier. This in my practice especially obtains in the large proportion of the student age group on my present list, but it depends, of course, upon the type of practice; we adapt our methods to the needs of our patients.

The second point is the great value to the Final-year student of spending a short time with a family doctor. They do not come to us to learn medicine, but we have something to teach them of the doctor-patient relationship, and especially I think in the case of the patient with the apparently unimportant complaint.

Our long-term friendship with our patients is new to these students. They are surprised and interested to realize the importance of geriatrics in general practice, an experience which they do not often meet in hospital. Family practice is in these and other essential ways so different from hospital practice, and is quite an unknown art to the student.

Sigmoidoscopy in General Practice

By KENNETH C. HUTCHIN, M.D.

THE sigmoidoscope is not, I believe, in common use in general practice, and, in fact, its use as a consulting-room or bedside instrument is comparatively rare in consulting practice. And yet it is a diagnostic instrument of great value which will reveal disease at an earlier stage than radiography and in a much wider area than digital examination. Direct vision —inspection of the part with one's own eyes—is the most certain method of examination providing one knows what one is looking at. Skill in the use of the instrument and training of the eye go hand in hand, and they can only be gained by practice. Like so many things once skill is acquired its value becomes more obvious day by day. I will not pretend that I use the sigmoidoscope daily or even weekly, but the same might be said of the ophthalmoscope. If, however, one can say, "In the past ten years I have prolonged the life of one man by diagnosing carcinoma of the bowel at a curable stage," I think one has made a case for the use of the sigmoidoscope in general practice. Cancer of the lower bowel is not a painful condition and it does not bleed in its early stages when there may only be a little persistent diarrhœa or rectal discomfort. If one knew that one could

examine a case safely with the sigmoidoscope with the expenditure of less than half an hour of one's time, would one not be likely to do it at a much earlier stage than one would send the case to a consultant?

The sigmoidoscope is a metal tube 30 cm. long with an obturator and a light. A glass window can be put on when the light is in position. In general practice I use the light plugged into my auroscope battery. There is also an air pump which can be used for inflating the bowel ahead of the advancing sigmoidoscope. One also requires a pair of long alligator forceps for swabbing areas of mucous membrane clear and for taking specimens.

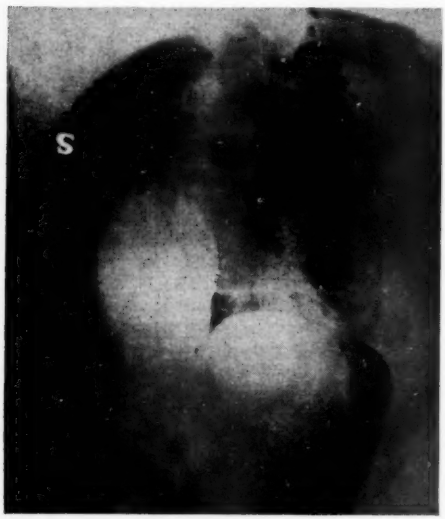


FIG. 1.—Radiograph of a barium enema held up at a stricture in the sigmoid colon.

How, one might ask, can a straight tube 30 cm. long be passed into the bowel which is certainly not straight? The bowel is fixed up to the second valve of Houston and the level of this valve is really the only fixed point and acts as a pivot on which the instrument is manipulated because below it the anal canal and rectum can be stretched and above it the bowel has a long, mobile mesentery which will enable the colon to be brought into a straight line. Fig. 1, which is a very old X-ray which was exposed to a tropical climate for many years, will give some idea of the range of the instrument. It shows a barium enema held up at a stricture in the sigmoid colon. I have frequently had the end of my sigmoidoscope against this stricture and finally, after dilating it, I passed the sigmoidoscope through it.

The only preparation of the patient required in the majority of cases is that he should have defæcated shortly before the examination. Purgatives and washouts are a disadvantage with which some surgeons habitually hamper themselves. Both of these alter the appearances of the mucous membrane and make the procedure more uncomfortable for the patient and difficult for the operator. If there is likely to be any difficulty about emptying the bowel purgatives may be given two or three nights before the examination but not the night before. It is important that one bears in mind and impresses on the patient that this is only an examination and not an operation. I have not always got that impression from the writings and conversation of surgeons. Of course, it is sometimes necessary to give a washout. This is a pity because a bowel washout not only removes some of the pathological appearances it is necessary to see (such as mucus, blood and pus) but also makes the normal appear abnormal. A normal mucous membrane looks more red and slightly œdematous and secretes more mucus after a washout of plain water or normal saline. In every case it is an advantage to catch a glimpse of the mucous membrane without a washout and also to see to what extent the bowel is capable of emptying itself unaided because this in itself may give you the diagnosis. If the bowel is loaded it is usually better to repeat the examination on another day. The patient will not object to this if there was no pain or discomfort the first time.

For the patient's comfort it is important to pass the instrument without inflating the bowel, or only doing so as little as possible. To pass the sigmoidoscope in this simple and safe way the position of the patient is of paramount importance. The patient must be in a true knee-chest position, with his knees placed apart on the very edge of the bed if you are doing it in his bedroom, or the end of the couch if you are doing it in the surgery. The buttocks should be swung slightly towards the examiner and the back must be arched down towards the bed. In this position the sigmoidoscope with the obturator in position is passed gently through the anal canal forwards and slightly downwards. Immediately the instrument has passed the resisting internal sphincter the obturator is withdrawn and the light inserted. The instrument is then directed by vision to follow the lumen of the bowel —forwards and upwards, then slightly towards the right and downwards, then to the left again to enter the sigmoid colon. The mucous membrane of the bowel is examined at all stages of the operation, both while inserting the instrument and while withdrawing it.

The instrument must only be advanced along the lumen where this can actually be seen. It is dangerous to push the instrument in any given direction at any point. I have performed this examination several thousand times and have seen a very large number of variations in the course of the bowel. There are times when one sees no clear road ahead. On these occasions one should withdraw the sigmoidoscope one or two inches and then advance again, and one sees that one has missed a turning or that the closed bowel opens up before the instrument. Never must any force be used. The instrument really advances by its own weight.

The normal mucous membrane is of a light pink colour, smooth and glistening. In the lower rectum the colour is darker and the texture is granular and in this area the submucous vessels cannot be seen. In the upper rectum and in the sigmoid colon, the mucous membrane is paler and the submucous vessels can be seen clearly.

[Coloured plates illustrating normal and pathological sigmoidoscopic appearances were shown.]

Menstrual Histories

By L. CARLYLE LYON, M.B., Ch.B.

WE all know how difficult it is to arrive at an accurate menstrual history. The remark "I am always regular, doctor" invariably leads me to ask "What do you mean by regular?" Then out comes the patient's diary and a careful search through it reveals the fact that the cycle is anything but regular. After years of this mental torture, sitting patiently while the search is continued (often wishing that the diary had been left in another handbag) I hit on the idea of letting the patient do her own "homework", and I devised a double-sided chart (part reproduced from Lyon, 1949, by kind permission).

DATE NAME AGE PARA S.M.W.S.D. R12.*

TEL.: ADDRESS MISCARRIAGES: OCCUPATION

Date of ONSET (a.m. or p.m. and day of week)	Duration Profuse, Normal or Scanty	Pain: (present or absent and when)	Number of days since previous ONSET	Changes in health or routine of life	Remarks (e.g. emotional upsets) and Treatment (if any)

*Single, married, widow, separated, divorced, re-married once, twice.

[For use by EVERY woman between 15 and 50 years of age.]

P.T.O.

Date of ONSET (a.m. or p.m. and day of week)	Duration Profuse, Normal or Scanty	Pain: (present or absent and when)	Number of days since previous ONSET	Changes in health or routine of life	Remarks (e.g. emotional upsets) and Treatment (if any)
Typical examples of how entries should be made on the other side :—					
1948					
Th. a.m. Jan. 1st	N. 4½ days	—	28	—	—
W. p.m. ,, 28th	N. 4 days	—	27	—	—
W. p.m. Feb. 18th	P. 7 days	+ 1st day	21	Severe cold started Feb. 11th.	Bad news on Feb. 9th
Th. a.m. Mar 18th	N. 4½ days	—	29	Fit again.	Aspirin grs. 10 ,, 18th Took a tonic
Explanatory Comments :—					
It is always convenient to know the date, or the day, on which periods commence; so one should be careful to record this ACCURATELY.	Periods normally last 4 - 5 days, but this varies in different individuals, and on different occasions in the same individual.	Pain is very often absent; but, if present the fact should be indicated by + or + + and when it occurs.	The 'cycle' varies considerably even when one is in apparently normal health. Question cause when it does !	Periods are often affected by illness or changes in one's environment. Any variation may or may not, be of importance ASK YOUR DOCTOR	Emotional influences may affect a period without apparently affecting one's general health. WITH APPROPRIATE ADVICE, AND PROPER TREATMENT, MUCH CAN AND SHOULD, BE DONE TO CORRECT IRREGULARITY.

Published by H. K. Lewis & Co., Ltd., London. "TABULOPERIOD" Chart. Copyright

It is my experience that the average intelligent woman readily co-operates in filling in her chart accurately. I let them supply me with as much data from past diaries as they have in their possession. Thus, on the second occasion on which the patient calls at the surgery, she is armed with sufficiently accurate facts to form a useful background.

A study of these figures reveals the most astonishing state of affairs—young, healthy-looking women often having a most irregular cycle, while others (in their forties or over, and looking ill) are surprisingly regular.

One can often, from an interpretation of the figures, be guided in the form of treatment.

General practitioners may be interested in research which the West London Faculty of the College of General Practitioners is at present undertaking.

The following points are of interest: (1) At what age does the average normal British girl mature? (2) Is there a difference between her maturing age and that of other nationalities? We have now many coloured people in our midst; how far do these differ from British girls?

In the case of *girls under* 15, it would probably be necessary to obtain the co-operation of the teachers as the girls themselves could hardly be expected to keep their charts accurately.

Next, the *age group* 15–20 *years*. It is my experience these charts require frequent scrutiny to see if they are establishing a normal rhythm; and, if not, what treatment is called for. Are they anæmic? Are they working too hard at school? Are they taking too much physical exercise, or not enough? Do they need glandular treatment? Are they ovulating regularly? Or is their menstrual loss of the anovular type? It is my contention that most of these conditions can be diagnosed from a careful study of their charts from time to time.

The *age group* 20–40 *years* are on the whole the most regular, but these again present their special problems. Here we are dealing with the *unmarried*, those *about to be married*, and the *married woman*. The unmarried woman who thinks she is a few days "late" with a period comes along in anxiety, and often reference to her charts of previous years reveals that this is not unusual for her. Those about to be married consult their charts carefully before fixing the date of their wedding—often to find, alas, that they have fixed the date unwisely or inconveniently.

The married women may be divided into those who are anxious to have children and those who are not; and here the question of the so-called "safe period" arises. Few women know how to calculate their approximate date of ovulation, and in this connexion I find the use of a chart indispensable. I always teach that ovulation occurs approximately fourteen days before the next *expected* period and bears little relation to the past period. Each woman, in normal health, appears to have a cycle peculiar to herself, and so the date of ovulation, approximate though it be, is not hard to determine; but we have to bear in mind that environmental and emotional influences, even more perhaps than changes in health, upset ovulation. And so the "safe period" can be anything but safe—in fact, in my opinion, it is a misnomer. One of our problems for research should be "to what extent is menstruation disturbed by these influences?"

We come now to the most difficult group of all—*the over* 40's. They call for close attention to our charts. When a period is overdue, how is the fact to be interpreted? Is the patient, whether she be married or not, an expectant mother? Or is she about to start the menopause? Among the questions I ask is "At what age did the periods begin?" And here I find that practically no woman realizes that the earlier she began the later will she finish having periods. Reference to the following figures will illustrate better what I mean. Are these figures accurate? Is this not a fit subject for research?

Age in which Menstruation Appears	*Menopause Should Occur*	*Age in which Menstruation Appears*	*Menopause Should Occur*
10 . .	Between 50 and 52	16 . .	Between 38 and 40
11 . .	Between 48 and 50	17 . .	Between 36 and 38
12 . .	Between 46 and 48	18 . .	Between 34 and 36
13 . .	Between 44 and 46	19 . .	Between 32 and 34
14 . .	Between 42 and 44	20 . .	Between 30 and 32
15 . .	Between 40 and 42		

Treatment during the menopause is difficult. I am convinced that the patient should NOT be told "she must put up with it", when so much can be done (and not by phenobarbitone only) to help her.

These menopausal patients, I find, keep their charts very faithfully. I can recall many years ago suspecting carcinoma of the uterus from the character of the chart—a diagnosis which was later confirmed by surgical measures and effectively dealt with.

And then lastly how do we know when the menopause is complete, and the married woman need no longer adopt precautionary measures? Pregnancies have been reported up to the age of 53; and I vividly recall that my first confinement in private practice was the case of a woman of 48 years who had been married fifteen years and had not previously conceived. That child is now 27 years old and is herself contemplating matrimony.

It will save a lot of time and trouble in dealing with women and girl patients if we advise them to keep their own personal charts, *and to keep them accurately*!

REFERENCE.—LYON, L. CARLYLE (1949) *Brit. med. J.*, ii, 1413.

[*April* 18, 1956]

DISCUSSION ON THERAPEUTIC RESEARCH

VIEW OF A GENERAL PRACTITIONER, A UNIVERSITY PROFESSOR AND A PHARMACEUTICAL COMPANY DOCTOR

Dr. G. I. Watson:

The Point of View of a General Practitioner

The first point I want to make about all therapeutic research is that it should be undertaken primarily for the good of the patient.

I shall start by surveying the field of therapeutics, and by measuring the intensity of the demand for research, and then try to define some of the difficulties and handicaps which a general practitioner encounters when working on a problem alone. I shall then point to ways in which such research might be developed, both by those who prefer to work as individuals and by others who find it more congenial to work in a team.

In general practice a high proportion of the drugs prescribed are given, not as cures, but to alter the sensations of disease as it takes its natural course towards recovery or the grave. Recently I took stock of my own therapeutics in a country practice and found that out of about 1,400 tablets which I dispensed in 1955 more than half were for the relief of three common complaints: 13% were for pain, 15% for sleeplessness and about 30% for the treatment of disorders associated with worry or anxiety.

The opportunity for therapeutic research in general practice covers every aspect of the life of an individual, from pre-natal care to comfort and support at the approach of death. It is the privilege of a general practitioner to bring his own interpretation of scientific medicine into the homes of his neighbours and friends at all stages of existence: to him, his patients are individuals and not cases or units or decimals per cent.

The demand for therapeutics comes from the patient; the demand for research comes from the doctor when dissatisfied with the treatments at his disposal. A great deal of therapeutic research is going on all the time in general practice; only a fraction of it is ever published and an even smaller proportion is planned research. Each of us has experienced that glimpse of a Higher Wisdom, but few of us have overcome the difficulties and handicaps which lie between our glimpse of the distant prospect and its attainment.

In general practice many of the commonest diseases tend towards spontaneous recovery. This blunts the incentive for research which is offered by incurable disease. In diseases for which no cure is known but from which spontaneous recovery is the rule, like the common cold, or from which it is extremely rare, as in cancer, therapeutic research meets its next great difficulty—that of providing adequate controls. It must learn to distinguish between alterations in the progress of a patient's illness due to natural causes and those due to drugs. The *vis medicatrix naturæ* of ancient writers, on which so many reputations have been built and so much therapeutic research has come to grief, is still possibly the most potent agent for recovery from illness, particularly in general practice. In several chronic diseases, as for example disseminated sclerosis, or rheumatoid arthritis, the natural variations in their course are often greater than those produced by beneficial drugs. I have her self-recorded figures for the daily variations in speed of movement of a patient with disseminated sclerosis which she began for me in 1952.

The third difficulty is one of accurate measurement, of comparing the effects of a single drug on different people, or the effects of different drugs on the same person at different times. Furthermore, one's therapy may often include medicinal and physical remedies as well as nursing, and it is seldom easy to decide which has contributed most to a patient's recovery.

Where a natural recovery is the rule the duration of illness in different patients varies, whether drugs are used or not; and when is convalescence complete? In the chronic incurable diseases only improvement or prolongation of life can be achieved, but both are difficult to measure. Where so much of our treatment is given for relief of the bodily sensations of disease, such as pain, sleeplessness, worry and anxiety, we are, of necessity, forced to rely on our patients' own testimony about the degree of relief afforded by drugs. We need to devise ways of comparing one man's sleep with another's or of measuring the amount of relief from their indigestion which, say, a miner and a bank-clerk each obtains by taking equal doses of the same powder. Such difficulties in devising accurate measurement are inherent in all medical research but are peculiarly acute in general practice, because here the end-points are not usually precise, like the concentration of a drug in the serum or the date of discharge from hospital, but more diffuse, like the recovery of a sense of well-being, the relief from pain, or sleeping better, having a better appetite or less indigestion.

The fourth difficulty is what I call the "irregularity of opportunity". The rate of turnover in general practice is often very slow and it might take several years for a country doctor to collect a series of patients with, for example, dysmenorrhœa treated by a new drug. Even with an investigation into the treatment of some common epidemic disease like measles, time is a hard taskmaster. A sudden rush of work during the winter can upset the regularity of our records about chilblains, yet we cannot investigate chilblains at the height of summer when the practice is quiet. However carefully we keep our records about National Health patients, when someone moves from our district or dies the records are recalled and we lose them, unless they are kept in duplicate. Our satisfied patients stay away and we must seek them out if we wish to measure their improvement; our dissatisfied patients change their doctor and are not particularly willing to co-operate.

There is now a fashion as well as a demand for therapeutic trials in general practice. We ought first to give some thought to the manner in which these may need to differ from similar trials carried out in hospital. The first necessity is for an accurate definition of the aims of the investigation. For example, when a new hypnotic is introduced to general practitioners for clinical trial, their aim would be to determine its relative place and usefulness among the hypnotic drugs already in common use. To examine the range and relative importance of the toxic side-effects of a new drug does not seem to me a particularly suitable aim for planned research by general practitioners, but an accurate description of toxicity when encountered unexpectedly should always be recorded in our notes.

Here I would like to make a distinction between a doctor's use of drugs for his sick patients as the best treatment which he knows for their condition, and his experimental use of drugs in volunteers whether they be sick or healthy. In this connexion I believe there is considerable legal difficulty in establishing whether a layman has, in any particular instance, the necessary knowledge to appreciate fully the consequences of consenting to be a volunteer for a new line of treatment.

The effects of a new drug are sometimes tested by a so-called "blind trial", in which the doctor observing the response to treatment is intentionally kept in ignorance of whether a particular patient is receiving the trial drug or a control. Such a doctor is really acting as an assistant to those who planned the test. A family doctor who is in general practice as a principal could ethically be in some difficulties about taking part in such a trial, unless he had a share in its design, since he is personally responsible to his patients for the treatment which he prescribes for them. Within the same ethical limits (Green, 1954), an assistant could act as observer for his principal and a single-handed practitioner could plan his own "blind-trials", if he, in turn, had help from a nurse or relative as observers.

In dealing with new drugs a distinction should also be drawn between a general practitioner's use of an unfamiliar drug on the advice of a consultant, as the proper and necessary remedy for the patient, and his use of a drug with which he is unfamiliar as part of a clinical trial on patients, whether volunteers or not. It is one thing to use a familiar drug as a new line of treatment in some particular condition; it is quite another matter experimenting with new drugs on our patients as though they were guinea-pigs. Over and above this a general practitioner must be prepared to justify his experimental use of any drug, both as regards its cost to the patient or the State and with respect to the duration of his patient's disability on the new treatment as compared with that on an accredited remedy. In the end, perhaps, only self-medication really fulfils all the requirements of the volunteer's knowledge, co-operation and consent!

The golden rule for us as general practitioners should surely be: "investigate but beware of experimenting." Even within these strictly ethical limits there is still room enough for observational research, particularly into the action of drugs which are used in the common infectious fevers, during convalescence, or for the comfort of those who are dying.

Turning now to the subject of records, there is need for further research into means whereby general practitioners may collect statistically useful information about their patients' response to treatment. One method, which has been developed particularly by Professor Hogben of Birmingham University (Hogben, 1953, 1954), is designed to use a patient's self-recorded information about his own activity while under treatment, and at the same time to provide carefully devised checks of his reliability as a witness. Where so much treatment is given for the sensations of disease, it is particularly valuable to have a method of measurement based on subjective reports. Sequential analysis (Armitage, 1954; Kilpatrick and Oldham, 1954) is another device which may eventually help general practitioners, since, by its use, the effectiveness of a drug may sometimes be demonstrated on relatively few patients.

In the case of the controls used for clinical trials in general practice, I suggest that inert substances should be used less often; whenever possible a direct comparison should be made with other accredited remedies commonly used for the disorder in question. In the treatment of a condition for which active drugs are usually prescribed, it is seldom as useful to

general practitioners to show how a new drug compares with an inert substance, as it is to test it against, say, two or three other active agents in common use, even if these are made by a rival firm. An inert substance is not quite the same as a "placebo". The latter, as its name implies, is intended to please the patient by means of its delightful colour and consistency and its objectionable taste; the former by deceiving the patient is really meant only to please the statistician. It is precisely in diseases from which spontaneous recovery is the rule that therapeutic research can make use of the placebo as a standard treatment against which the activity of a new potent remedy may be measured. Surely an allegedly active tablet could be tested against a delectable liquid placebo without either deceiving the patient or upsetting the statistical value of the trial.

Collective investigations, particularly with mechanical aid in analysis, can be one means whereby general practitioners overcome their difficulties of isolation and infrequent cases. For example, if several doctors are working to a common plan, in which each uses a treatment of his own choice for the condition under review, then the relative value of several different treatments may be compared directly with one another, without recourse to any inert controls. The protocol of such an investigation may be drawn up by one person or by a small group, and the work done by the group alone or with assistance from other doctors who had no share in the planning. Help with design and analysis may be sought from a University department or a drug firm; on the other hand manufacturing chemists, and members of hospital and University staffs are now bringing their own problems increasingly to the notice of general practitioners, with requests for comments and collective assistance in carrying out their proposals. Some drug firms have gathered the names of a number of general practitioners who are willing to help them in clinical trials. This two-way traffic is an encouraging recognition of the special knowledge which can only be gained in general practice, and we may soon see collective investigations, jointly planned by all three partners to the enterprise of therapeutic research.

My late chief, Dr. Colin Lindsay, a past President of the B.M.A., used to say that every general practitioner died with at least one good hypothesis uncommunicated to the world. If one of these were connected with therapeutics, to whom should he first have turned for help? Any doctor can write to the Medical Research Council about his proposals for research. Some doctors keep in touch with their medical school or University, and a few are lucky enough to have established personal contact with the research department of a manufacturing chemist, either by chance or over some particular problem. General practitioners themselves have created various means of making collective contact with one another, in order to share their experience and opportunities. I believe, however, that over and above all this there is need for a Research Centre, representing the whole pharmaceutical industry, to which any doctor, whether in general or hospital practice, can bring his therapeutic problems.

To such a Centre, if it existed, I would bring the following problem, about which I have been concerned for some time, namely the massive use by the public of aspirin and related compounds in infectious diseases. There is a well-documented resemblance between the action of aspirin and the action of cortisone in patients with rheumatoid arthritis (Kellgren, 1952 and M.R.C., 1954). Also cortisone reduces the reaction of the body against parasitic infection (Thomas, 1953, and Editorial, 1954); but has anyone ever shown whether aspirin also has this precise effect? (Coste *et al.*, 1953.) For example, does aspirin, like cortisone, increase the susceptibility of healthy Rhesus monkeys to infection by poliomyelitis virus as in the safety tests for the new vaccine? If not, this difference between the two drugs might prove a useful starting point for further research. If it does, then we must surely warn our patients against their indiscriminate use of aspirin for pyrexia of unknown origin during the summer and autumn months, when poliomyelitis is prevalent. What about the routine use of aspirin in tonsillitis? Would anyone prescribe cortisone gargles for such patients? Or again have aspirin compounds, like cortisone, any special danger for those who knowingly or unknowingly have suffered a tuberculous infection in the past? Evidence about these points will be difficult to collect in human disease, and a trial of aspirin in acute sore throat might be the easiest to arrange; meanwhile experiments could also be undertaken with laboratory animals and possibly with tissue cultures to see whether aspirin will lower the minimum lethal dose of infecting organisms or increase the susceptibility of tissue cultures to infection by viruses.

This whole matter of the use of aspirin compounds to suppress the symptoms of parasitic infection is one of considerable importance to the public health and calls for a joint investigation far beyond the capacity of any one general practitioner to organize. It is however, I am sure, only one of many such problems which have been studied by general practitioners and I believe it would be worth creating the means whereby this store of incomplete or unpublished hypotheses could be brought to light for the benefit of medicine and mankind.

REFERENCES

ARMITAGE, P. (1954) *Quart. J. Med.*, **23**, 255.
COSTE, F., BOUREL, M., DELBARRE, F., and WEISSENBACH, R. (1953) *Pr. méd.*, **61**, 979.
Editorial (1954) *Brit. med. J.*, i, 381.
GREEN, F. H. K. (1954) *Lancet*, ii, 1085.
HOGBEN, L. (1953) *Brit. med. J.*, ii, 163.
—— (1954) *Med. Pr.*, 232, 331.
KELLGREN, J. H. (1952) *Brit. med. J.*, i, 1152.
KILPATRICK, G. S., and OLDHAM, P. D. (1954) *Brit. med. J.*, ii, 1388.
Medical Research Council and Nuffield Foundation (1954) *Brit. med. J.*, i, 1223.
THOMAS, L. (1953) *Ann. N.Y. Acad. Sci.*, **56**, 799; *see also* (1952) *Ann. Rev. Med.*, **3**, 1.

Professor J. M. Mackintosh:

The Point of View of a University Professor

"If continuity of observation is of the essence of medical science, then the general practitioner must be a member of the investigative team without regard to his possession of personal creative endowments."

This comment of Dr. E. M. Bluestone, in his annual letter to the Hospital Administrators Correspondence Club, lies at the heart of his plea for greater co-operation between the hospital and the general practitioner. We should begin by recognizing that continuity of observation *is* of the essence of scientific therapeutic research; and it follows that the general practitioner, who has unrivalled opportunities for continued observation over the years, ought to be a full member of the research team. It is not essential that he should be personally endowed with a capacity for original work. The main features that I discern in surveying my subject and focusing rather narrowly on the terms of reference, are the outstanding opportunities of collaboration between general practitioners and an academic body undertaking or guiding field research. For this reason I do not propose to make more than a passing reference to fundamental laboratory investigations, or to therapeutic research carried out by either University departments or the great pharmaceutical firms.

I. The Contribution of an Academic Institution

(1) *Fundamental research.*—Our first question is to enquire in what way an academic body can best collaborate with the general practitioner in his field studies. To begin with, certain purely physiological researches, including the use of animals for fundamental work, may unfold a bodily process or mode of action that points the way to a possible line of treatment. On the other hand pure research in the University tends to be remote from the practical issues of everyday medicine. It is right that the University should devote itself to research for its own sake but there would be great benefits in relating the findings wherever possible to extra-mural activities. In this way a hidden link may sometimes be revealed. Pathological and bacteriological researches may disclose lines or modes of action that had not been hitherto understood and their findings may suggest new field trials to demonstrate the efficacy or otherwise of changes in the method of application. Recent discoveries in relation to immunizing agents may create valuable pointers to methods of prevention and long-term observation. Similarly recent fundamental work on the heart and the cardiovascular system offers a wide range of opportunity for both prevention and therapeutic follow-up.

In the second place, University departments have unique opportunities for what is rightly called *experimental medicine*, that is, the correlation of laboratory research with clinical trials under hospital conditions. This affords the ideal environment for strict scientific control, and in this sphere I think that surgery has taken the lead. One remembers at once the admirable experimental work on the heart and the blood vessels, the lungs, and the brain. In clinical medicine and its auxiliaries an increasing amount of attention has been paid to experimental work, notably in relation to blood pressure, the liability to thrombosis, and many problems of nutrition. This is all to the good, so long as experimental medicine continues to observe its ethical obligations to patients. It is all to the good, but it is far from complete. It has often happened that, after a drug or a particular form of treatment has passed through exhaustive trials under experimental conditions in both laboratory and hospital, certain characteristics which are undesirable or even dangerous, come to light only in the broad acres of general practice. Then reports on various side-effects, observations of a falling-off in potency frequently associated with bacterial resistance, sensitivity reactions and the like, begin to trickle through the medical literature. The general practitioner is usually in a very favourable position to note these special effects,

and many original observations owe their origin to his acute senses and his human experience. It is clear that the contribution of the academic institution is a two-way process; and we neglect the return channels at our peril.

(2) *The planning of research.*—Universities, Colleges, and Research Institutions generally have a great responsibility for planning. The waste of time and human effort that can be involved through an ill-planned study is colossal, and it is for this reason that bodies such as the Medical Research Council and the Public Health Laboratory Service have a valuable function in taking the initiative. Such methods apply especially to organizing field trials, for example, when a new immunizing agent is introduced and is designed for use on a large scale. It may be that the planning process is unduly slow and cautious, when life-saving is in issue; but it is better to be safe than sorry.

Planning, however, means far more than organization—it usually involves selection from a number of exciting projects, or of rival methods in a single project. It always requires an expert to prepare the design and to apply rigid statistical tests to ensure validity, whatever the outcome may be. Good planning in a new venture must also take economic considerations into account, because skilled husbandry of resources is much more than a mere striving for cheapness. The cost in human effort is more serious than the financial expenditure, but both are important. Another point, often forgotten in the planning of research on a large scale, is that the work should be as stimulating as possible for those who take part in it.

University departments are specially fitted for the planning of original research, because of the effective co-operation between departments—statistical and operational—and their capacity for pilot experiment. In the Universities and academic institutions lies the best opportunity for that supreme quality of detachment. It is important to see that this does not take refuge in isolation.

(3) *The evaluation of research.*—Original research may bubble up, clear as crystal, from any spring, however small and remote—a cider vat in Devon, a farm in Gloucestershire, a Yorkshire Dale, or a drab town in Lancashire. Planned scientific investigations tend to be the function of a University, an *ad hoc* Institution, a large industrial Organization, or a voluntary Foundation, not infrequently deriving its resources from a successful industry. The evaluation of research, however, demands a different kind of composition in which the outstanding qualities are freedom from bias, so far as that is humanly possible, immunity from political interference or commercial pressure, and a widely informed critical faculty. It is not necessary that the members of the evaluating body should be specialists in any compartment of research, although of course they would be guided by appropriate experts, at any rate in statistics.

The right evaluation of a research project depends not a little on a judgment of the personality of the promoter and a general knowledge of the field in which he works. One would expect, therefore, that some of the members of a committee appraising an industrial scheme for research would have a broad knowledge of industrial conditions, in the same way that field studies to be undertaken by general practitioners would be reviewed by a group, some of whose members had a sound and active experience of the scope and limitations of general practice. In my view the evaluation and supervision of research work undertaken by general practitioners in the field is a true function of the College of General Practitioners, operating through its Research Committee. This is not to say that all projects of research in general practice ought to be initiated by the College. On the contrary, they will, I hope, continue to arise on the initiative of such institutions as the Ministry of Health, the Medical Research Council, the Universities, the voluntary Foundations, and the pharmaceutical profession. Nevertheless I do feel strongly that the College of General Practitioners should be the recognized clearing house for all research to be undertaken by general practitioners. The College, as an academic and non-political organization, is best fitted to offer guidance to its members, to watch over the development of projects, and to advise caution, when there is a risk of overlapping or, worse still, overloading.

In the assessment of research projects, epidemiological and clinical, the University has important advisory functions; it has to set up criteria of therapy which are scientifically acceptable. That does not mean therapy in terms of cure. The definition goes beyond these limits into the realm of prevention in considering, for example, immunization procedures; and it cannot ignore the effect of measures, by the exhibition of drugs or otherwise, which are purely symptomatic.

A controlled clinical trial of a new remedy is usually carried out in one of two ways: In the first we decide beforehand to take into the trial a *fixed* number of patients who will be allocated in a random order (1) to the customary treatment of the day and (2) to the new treatment under test. A comparison of the results is then made.

In the second way, no previous decision of the size of the trial is made but we take

patients into it, allocating them randomly as before and stop the trial merely when it is thought that a sufficient number has accumulated. Again the results at this point are compared.

A more modern method (now itself under test in various trials) is based upon *sequential* analysis. This method allocates patients admitted to a trial in pairs, one being given the customary treatment and the other the new treatment (the order is randomized for each pair). The relative result of the two treatments is noted for each such pair of patients and these results are *continuously* summarized. We thus find *step by step* whether treatment A is proving better (or worse) than treatment B—or whether there is no effective difference between them.

This method of watching the results as they come in enables a conclusion to be reached earlier (*on the average*) than with the previous methods of a fixed (or unfixed) number of patients. It has, therefore, a general advantage in saving labour, &c., and an ethical advantage in revealing the superiority of a certain method of treatment at the earliest possible time.

To be wholly effective the method requires some clearly defined event to differentiate the results under the two treatments, e.g. death or recovery within a given interval of time, a specific complication appearing or not appearing.

How far it is likely to supplant the previous methods is certainly not yet clear. It *is* clear that in some instances the sequential approach should be carefully considered while in others it seems unlikely to help and sometimes to present disadvantages.

When in doubt the non-statistically trained would do well to consult the statistician.

II. The Contribution of the General Practitioner

How can the general practitioner make the best contribution possible to the academic research department? For illustrative purposes the answer may be set out in a number of divisions:

(*a*) *Personally chosen therapy.*—A practitioner or a group set out to study the effects of a particular drug or mode of treatment. The essence of the research is long-term observation, and this is the very foundation of research in general practice. In some ways the observation of one's own treatment, and especially drug therapy, is full of pitfalls. Ideally, one should note down in a methodical manner the information gained day by day, without attempting to synthesize. In other words the aim is to accumulate evidence by some such means as plotting points on a chart, and postponing the view of the whole picture until the number of points is really sufficient to offer information. Here the doctor is sailing rather too near the sirens: the lure of the new, the decorative and the palatable. Needless to say, the observations and the dangers are not confined to drug therapy alone. They may cover other substances used to prevent or abort specific diseases. Included in this group are vaccines and antitoxins, and studies may be made on method and ease of administration, immediate and remote side-effects, protective value and its duration. Similar observations on substances like liver extract, insulin, the thyroid group, and a plethora of endocrine preparations, many of which may be prescribed over long periods, come naturally under the eye of the family doctor whose contact with, and intimate knowledge of, his patient places him in a relationship not enjoyed by any other member of the profession. Patients knowing their own doctors will often produce valuable information on their own responses to new or well-tried drugs, information which is more likely to be forthcoming in the privacy of the patient's home and the relationship of confidence between doctor and patient.

Many practitioners have an unrivalled knowledge of infants and young children in their home surroundings, and so add valuable information on the effects, not only of substances used specifically to prevent or cure diseases, but also that fringe of therapeutics which covers vitamins, food additives and replacements.

Another field of study in the realm of personal therapy allows the doctor to note carefully the use, efficiency, duration, and dosage of the countless drugs which have as their object the relief of pain, especially for the wan discomfort of the deathbed.

(*b*) *Observation of therapy, when the general practitioner is a member of a research team with his own colleagues.*—This arrangement has the obvious and very real advantage of enabling him to check his observations by comparison with those of others who are engaged in the same pursuit. In certain circumstances it provides the additional benefit of permitting a group of workers to make use of controls without losing sight of the ethical considerations involved. It is clear, however, that group research cannot be effectively carried out unless the information is fed, so to speak, into a common channel. It is here that a Research Committee can act so effectively as a storehouse in gathering and sorting

out information as it accumulates. Not only this, but it also examines conflict of opinion, and relates new facts to the main body of the findings. Again, the general practitioner frequently modifies recommended procedures of many therapeutic agents, because experience teaches him that they produce better results, or disturb the patient less, without jeopardizing the outcome. In such cases the value of group findings is considerable.

(*c*) *Observation of therapy which has already been provided in a hospital and is recommended, on the discharge of the patient, for continuation.*—In these days, when the policy of shortening the stay in hospital is gaining ground, follow-up of hospital treatment is invaluable. A series of simple checks is not enough; in the favourable conditions of home care it can and should become a deliberate investigation. The hospital will gain through the long-term study of its therapy and also by closer co-operation with the practitioner in charge of the patient. Yet this does not come of itself: the hospital must for its part be prepared to offer the basic conditions of research by providing the best information available, the opportunity for further consultation and, if necessary, facilities for special diagnostic procedures, or specialized treatment which can be given on an out-patient basis.

(*d*) *Observation of therapy advised by a consultant called in by the general practitioner.*—It is well known that the number and scope of domiciliary consultations is increasing rapidly.[1] Within proper limits this is a move in the right direction, but scientific control is an essential condition of success. Home consultations can easily go wrong in the sense that they fall into the dullness of routine, when each one should be a starting point for careful combined investigation. In this respect the consultant has probably more to learn than the practitioner: as Bluestone pointed out, it gives him "priceless insight, through the eyes and ears of the practitioner, into the environmental circumstances in which the illness of the patient was incubated". In this context the word "environmental" was not used in the narrow sense, but included all the family and social circumstances which surrounded the patient in his home.

(*e*) *Observations of therapy by means of a project instigated by a research institute, central department, &c.*—In this type of research the general practitioners are taking part in a planned reconnaissance. Their function is to make factual observations in accordance with an agreed schedule, and to send back from time to time the accumulated information to headquarters. The workers in the field are the agents of the authority which reaps the harvest. In research of this kind, especially in what are now called "controlled trials" it is vital that the practitioners should be partners in the work, fully informed of its progress, and not merely agents. For this reason among many others it is desirable that the organization of field research by general practitioners should be channelled through the Research Committee of the College of General Practitioners—and this is especially important when the scheme covers a wide area of the country.

Dr. Kenneth Carter:

The Point of View of a Doctor in a Pharmaceutical Company

My contribution will express the view of *a* doctor in a Pharmaceutical Company. I stress *a* doctor as the views will be my own and not necessarily those of the pharmaceutical industry or of the particular company with which I am associated.

The objectives and stages of research.—The aim of therapeutic research is to provide new therapeutic agents for the more effective treatment of disease. Three types of research are involved:

(1) *Fundamental research*—work concerned with natural phenomena in normal and in abnormal circumstances—in health and disease.

(2) *Applied research*—the search for substances which will modify physiological and pathological phenomena. From this may emerge compounds with specific activity but not necessarily a cure for a specific disease.

(3) *Development research*—the endeavour to relate applied research to clinical problems in order to evolve useful therapeutic agents. This may involve organic chemists, chemists interested in structure/function relationships, biochemists, physiologists, pharmacologists, bacteriologists, pathologists, statisticians, and other preclinical and clinical scientists.

For example, finding a sympathetic blocking agent which reduces blood pressure in normal animals and in experimental hypertension will lead to the synthesis and examination of many related compounds in the search for maximum efficacy and minimum toxicity. This

[1] Abel-Smith, B., and Titmuss, R. M. (1956) The Cost of the National Health Service in England and Wales. Cambridge; p. 128.

will cover studies in animals and in humans, and eventually pharmaceutical research will be undertaken to provide the active material in a stable form suitable for administration to patients.

Clinical Trials are part of the development effort. Once activity and freedom from toxicity have been confirmed in man, the effect of the compound must be determined in patients with different diseases.

Economic Production is part of the development effort. New discoveries cannot be of general benefit until supplies are freely available. At this stage organic chemists, chemical engineers, production engineers, and those with financial and business responsibilities consider how best to translate laboratory methods of preparation into large-scale synthesis and economic manufacture. This research is continued during the entire life of the product, and is reflected in price reductions such as have occurred with penicillin over the last ten years.

Concentration, complexity, costs and collaboration.—The university, the clinician and the pharmaceutical company each perform different functions. In fulfilling these functions they will each tend to concentrate on different activities. It is in the University that fundamental research has its real place as it is best undertaken in an academic environment not forced by commercial pressures which are inseparable from a business enterprise.

The Pharmaceutical Company will concentrate on the development and production of therapeutic agents. It has functions in common with other businesses and also functions common to research institutes. The business side must be efficient and profitable to the shareholders and contribute to the economic prosperity of the country. The research side is an investment for the future. The prosperity of the company depends on the success of research efforts. As scientific achievement advances, old therapeutic agents may become obsolete. The scientists are chosen for their ability to apply their efforts intelligently in such a way as may directly or indirectly lead to the discovery of new therapeutic agents; for economic reasons particularly those *with a wide application in clinical practice*. They expect to be able to work on interesting worth-while projects, to have first-class facilities, adequate funds and personal remuneration, and the opportunity to publish the results of their work at scientific meetings and in scientific journals.

The best scientists may well be found in academic life, but many of excellent calibre are now in the research departments of pharmaceutical companies. Several University Professors, Readers and Lecturers have, during the past ten years, been recruited from industry, and others of equal calibre have remained in, or left academic positions to go into, industry.

To carry out the development and production of useful therapeutic agents requires complex organization involving many department activities, using many different skills and a considerable investment.

The British pharmaceutical industry spends over £3 million annually on research and development which compares favourably with the Government expenditure through the Medical Research Council [1] in 1954–55 of £1,844,681 on the ordinary account and £102,428 on the non-recurrent account for special apparatus and buildings. The American pharmaceutical industry spends over £20 million per annum.

The major effort in Britain is undertaken by a few companies—I.C.P., Glaxo, Boots, Wellcome Foundation and May & Baker. The first three each spend around £500,000 p.a. The two companies with whom I have been associated, Glaxo and Smith, Kline and French Laboratories, each employ approximately one in five of their staff in research and development, and approximately one-third of these have scientific qualifications.

Sir Harold Himsworth [2], in the 1955 Linacre Lecture, spoke of the problems of Integration of Medicine and recognition that advancement of knowledge requires the bringing to bear of several different disciplines leading to the formation of teams of integrated experts.

Original observations by well-trained workers frequently provide the research ideas. However, the problems of pharmaceutical research are now so complex that collaboration from many scientific disciplines and from investigators with clinical facilities in hospital and in general practice is necessary. Rarely is the clinician in General Practice, or in Hospital, the University, or the Pharmaceutical Company in a position to carry a research project through all the stages which lead to the provision of a new therapeutic agent. It would seem worth while, therefore, considering how we can work together on research problems of mutual interest.

The most fruitful area for collaboration between the pharmaceutical company, the University, and the General Practitioner, lies in Applied Research and Development—

including clinical evaluation and economic production. In these areas industry needs, and can contribute, expert assistance.

Steps in the development of a new therapeutic agent.—A brief sketch of some of the steps which are likely to be necessary in the development of a new therapeutic agent will show how our efforts are complementary.

The basic lead invariably comes from fundamental research, and therefore the industrial research worker must be able to follow new advances by (*a*) Keeping in touch with the literature; (*b*) attending scientific meetings; (*c*) informal discussions with University and Hospital research workers, and by consultant arrangements.

However, the University scientist who realizes the practical possibilities in a new fundamental discovery may follow the lead through into applied research or he may bring his ideas to others working in applied fields.

This idea may lead the industrial organic chemist to synthesize several series of related compounds. The academic organic chemist may also do this if the synthesis of the compounds is otherwise of research interest, or if he is a member of a therapeutic team, but academic duties frequently prevent his work progressing rapidly, or at all. This also applies to the laborious screening work which now needs to be undertaken by biochemists, bacteriologists and pharmacologists in industry. However, the advice of academic workers is invaluable in establishing appropriate methods of testing, in the interpretation of the results, and in guiding the direction of research effort.

When at last a compound is found which passes preliminary pharmacological tests and in animals appears to combine maximum activity and minimum toxicity, industry must again seek collaboration with clinical investigators.

Experienced investigators with hospital facilities usually undertake preliminary studies to confirm action and freedom from undesirable side-effects, and therapeutic hypotheses are proposed. Difficulty may be experienced in locating clinical investigators interested in appropriate therapeutic fields, and work may progress slowly until publications stimulate enquiries and further work. These investigations then lead, if the results are favourable, to more extensive clinical trials in Hospital and General Practice.

General Practice often provides most important facilities for therapeutic research, and it is desirable for investigations to be carried out by General Practitioners before new therapeutic agents are marketed. The well-equipped research department of the pharmaceutical company is by no means a passive partner even in the stage of clinical evaluation as it may offer the clinician: (*a*) Further new research compounds, ideas, and interesting problems; (*b*) the fullest relevant information on aspects of previous research work; (*c*) supplies of drug and controls; (*d*) laboratory assistance and scientific collaboration; (*e*) grants appropriate to the work involved and for equipment if this is required; and (*f*) opportunities to discuss his research work with other investigators at all levels.

Some are also able to provide statistical assistance and help in the design of the investigation and in the assessment of results.

The decision to market a new compound should be based on objective information provided by well-controlled investigations, otherwise unjustifiably favourable research reports may easily lead to premature marketing. This may have unfortunate consequences for the patient and the physician. The pharmaceutical company may also suffer in loss of reputation and financially, as a considerable expenditure is required to produce and market a new therapeutic agent.

Some outstanding problems.—There is a need for collaboration but the main problem for discussion is how to achieve this. How do we get in touch with each other and learn of each others' interests?

Those of us working in the pharmaceutical companies have still to learn:

(1) How to become more familiar with problems which are important to the clinician and which are under investigation in the University, in the Hospitals and in General Practice.

(2) How to find, with the least delay when problems occur, investigators with whom we have a common research interest.

(3) How to obtain expert advice and representative medical opinions.

(4) The best methods of securing collaboration.

Should this be done on a basis of personal contact as at present, or can we organize ourselves more efficiently? Can the Royal Society of Medicine or the College of General Practitioners provide a forum for subsequent discussions? Are the Universities interested in meeting to discuss these problems? What incentive and assurances do academic research workers and General Practitioners need to establish closer collaboration? I should

certainly welcome the opportunity of talking with individuals and organized groups of investigators in General Practice, in Hospital and in the University.

The main functions of the Pharmaceutical Company are to use all available knowledge and skills for the development and economic production of useful therapeutic agents.

It is recognized that the efficiency and chances of success of therapeutic research carried out by pharmaceutical companies can be greatly increased by expert guidance, advice and collaboration from academic scientists, and research workers and clinicians in Hospital and General Practice. How to achieve this is a matter for discussion and consideration by all participants.

Pharmaceutical Companies may obtain the collaboration of academic scientist and clinicians by

Employing well-qualified scientists with whom academic scientists and clinicians are willing to collaborate.

Providing good research equipment and facilities.

Providing access to the literature and scientific advisers.

Liberal policies of collaboration and sympathetic understanding of the ethical standards of scientists and clinicians.

Seeking advice and collaboration when required.

Providing some complementary service, more valuable than money, to make collaboration attractive:

(*a*) Laboratory assistance—chemical, analytical, biological.
(*b*) Preparation of special chemicals.
(*c*) Testing facilities.
(*d*) Research compounds and interesting problems.
(*e*) Literature research facilities.
(*f*) Expert assistance in planning and design of clinical trials, and interpretation of results from a statistical viewpoint.
(*g*) Grants and research fellowships.

Collaboration *within* industry on research methods, organization, and on other common problems.

REFERENCES

1 *Rep. Med. Res. Coun., London*, 1953-54 (1955) p. 1.
2 HIMSWORTH, H. (1955) *Brit. med. J.*, ii, 217.

Clinical Section

President—Sir HENEAGE OGILVIE, K.B.E., D.M., M.Ch., F.R.C.S.

[*March* 9, 1956]

Hæmophilia with Small Bowel Obstruction Due to an Ileal Hæmatoma.—A. G. PARKS, M.Ch., F.R.C.S. (for S. H. WASS, M.S., F.R.C.S.).

L. B., aged 43, was a known hæmophiliac admitted on 13.3.54 complaining of four days abdominal pain.

His early childhood was punctuated by episodes of swollen joints and he was unable to play games. At the age of 12 a diagnosis of tuberculosis of the left knee-joint was made and was treated by immobilization for nearly three years. Aged 15 he was admitted to hospital for dental extraction. The disease was relatively inactive until he was 41 when a hæmarthrosis of the left elbow developed following a trivial blow.

He was one of four healthy sons; there is no known relative with a bleeding tendency.

About three months after the hæmarthrosis of the elbow his young daughter jumped on his abdomen. The next day he lost his appetite, was continually nauseated and vomited once. Over the next three days colicky abdominal pain increased in severity, he vomited many times and had complete constipation.

On admission to hospital he was found to have a normal temperature, a pulse-rate of 120 per minute and a respiratory rate of 22 per minute. His blood pressure was 140/110 mm. He was obviously very ill, with signs of dehydration and a furred tongue.

Examination of the heart and lungs did not reveal any significant abnormality.

His abdomen was distended and there was generalized rigidity. There was marked tenderness in the lower abdomen with rebound tenderness. The bowel sounds were high pitched and occurred in typical, obstructive rushes. Rectal examination was normal.

Other stigmata of hæmophilia included a stiff left elbow and subluxation of both knee-joints.

His abdomen was X-rayed on admission and numerous fluid levels and distended loops of small bowel seen. One interesting feature was overlooked, namely erosion of the right iliac crest by an old hæmatoma.

His hæmoglobin was 78%, the blood clotting time was 8 minutes (Dale and Laidlaw) (normal 1½ to 3 minutes).

Before operation he was given two pints of fresh blood which reduced the clotting time to 2½ minutes. Intravenous fluids were administered and a gastric tube passed.

After he was anæsthetized a mass was felt in the right iliac fossa and accordingly a transverse incision was made over it. This lump proved to be the retro-peritoneal hæmatoma previously referred to, the obstructing lesion being in an adjacent loop of bowel. The peritoneal cavity contained blood-stained fluid. A loop of dusky purple small bowel 12 in. long was delivered from the abdomen, it was swollen and obviously the lumen of the small intestine was obstructing. The adjacent mesentery was red and swollen. The appearance was that of a strangulated loop, though no cause for strangulation was found. Accordingly the lesion was resected and continuity restored by end-to-end anastomosis.

After operation gastric suction was continued for three days and for six days he received intramuscular streptomycin and penicillin. One pint of fresh blood was given daily for five days by which time his hæmoglobin was 114%. Fresh plasma was given after this for two further days. On the eighth day no blood or plasma was given and on the following day he had a massive melæna. His hæmoglobin fell to 42%. Blood was given until his hæmoglobin was within normal limits, after which plasma was used until the seventeenth day after operation. Altogether 15 pints of blood and 6 pints of plasma were given. His wound healed satisfactorily and he was discharged one month after admission. Subsequently he has been admitted to hospital three times for episodes of bleeding into tissues or joints.

After recovery from operation a more detailed hæmatological study was performed.

In addition to a prolonged clotting time, the prothrombin consumption was slow. A thromboplastin generation test revealed the deficiency to be in the patient's plasma, showing him to be a true hæmophiliac.

This patient is presented not so much to describe a rare complication of hæmophilia as to add a further case to the number already reported on whom major surgery has been performed. Provided that the clotting time is kept near normal limits no great operative problems are encountered. Experience with only one case suggests that fresh plasma (or the concentrated anti-hæmophilic factor) should be given for two to three weeks after surgical intervention. It is helpful to distinguish between true hæmophilia and Christmas disease, as in the latter, stored blood or plasma is effective in restoring the normal clotting mechanism. A thromboplastin generation test shows the serum to be deficient in a required factor in Christmas disease, in hæmophilia the plasma is deficient.

Polyarteritis Nodosa.—R. C. KING, M.D., M.R.C.P. (for E. R. CULLINAN, M.D., F.R.C.P.).

History.—A married woman, aged 29 years, had poliomyelitis twenty-three years ago which resulted in some shortening of the left leg. Following this she had whooping-cough, which was complicated by recurrent attacks of bronchitis and eleven years ago she had her first attack of bronchial asthma. Asthmatic attacks subsequently occurred intermittently and twenty months ago she developed an acute polyarthritis, affecting the knees, ankles, hands, wrists and shoulders. She was admitted to hospital, where a diagnosis of acute rheumatoid arthritis was made. While under observation, an apical systolic murmur appeared and a diagnosis of acute endocarditis was suggested. Treatment with penicillin and streptomycin was commenced, but following the appearance of a circinate erythematous rash, the diagnosis was changed to one of acute rheumatic fever. Fifteen months ago she developed a petechial rash on the hand and this was followed by left foot drop and weakness of the right hand. Thirteen months ago the asthma increased in severity and a high eosinophilia and raised E.S.R. were discovered. At this time an intermittent pyrexia occurred and this persisted until her admission to St. Bartholomew's Hospital eight months ago. Her father, two sisters and one brother were alive and well. Her mother and two aunts suffered from bronchitis.

On examination.—Underweight, ill, pyrexial. Fundi normal. Upper cervical lymph glands enlarged. R.S.: Diffuse bronchospasm. C.V.S.: Pulse 100, regular. B.P. 125/85. Heart size normal. Localized soft apical systolic murmur. Abdomen: Liver enlarged 3 fingerbreadths. Spleen enlarged to the umbilicus. Nervous system: Right ulnar and left lateral popliteal nerve palsies with muscle weakness and sensory loss. Joints: Peri-articular swelling affecting especially the small joints of hands. Some shortening of left leg. Skin: Acneiform eruption of face. Two raised petechial-like spots on dorsum of left hand.

Investigations.—Hb 70%. E.S.R. 79 mm. in one hour (Westergren). R.B.C. 4,320,000. M.C.H.C. 30%. M.C.V. 81 cu.μ. W.B.C. 12,800 (polys. 26%, lymphos. 29%, monos. 4%, eosinos. 41%). No immature white blood cells. *Sternal marrow:* Marked activity of the eosinophils but no evidence of leukæmic reaction. *Stool:* No cysts, ova or pathogens. *Sputum:* Contained eosinophils. No arthropods. Culture grew coliform bacilli and non-hæmolytic streptococci. No A.A.F.B. *C.S.U.:* Trace of protein, excess of leucocytes and *moderate numbers of red blood cells. Blood culture* sterile. *Casoni test:* Negative. *ECG* normal. *X-rays:* Chest: lungs clear. *Intravenous pyelogram:* Good renal function; ? right renal calculus. Sinuses: Gross opacity of left antrum. *Urea clearance:* 65% and 84% of average normal. *Skin biopsy* (lesion of the back of left hand)*: Allergic vasculitis.*

Treatment and progress.—While in hospital the pyrexia continued and she had repeated hæmoptyses for which no cause could be found. Treatment with cortisone was commenced: 25 mg. t.d.s. by mouth with dramatic response. The fever settled, the asthma resolved and the E.S.R. fell to 19 mm. in one hour. Five months ago she was discharged from hospital on a maintenance dose of cortisone 12·5 mg. t.d.s. Through a misunderstanding the cortisone was discontinued and four months ago she was readmitted, having suffered an episode of subarachnoid hæmorrhage in another hospital. There were signs of right middle lobe collapse with diffuse bronchospasm and the blood pressure had risen to 150/110. Urinalysis and urea clearance were both normal. The asthma was controlled by temporarily increasing the dose of cortisone and the collapsed lobe re-expanded spontaneously. She left hospital again on a maintenance dose of cortisone 12·5 mg. t.d.s. When seen one week ago she was well. Examination revealed minimal bronchospasm with a blood pressure of 140/85. The liver was no longer enlarged but the spleen was just palpable. There was definite improvement in the ulnar sensory loss but little change in the weakness of the right hand or left foot. Urinalysis, blood urea, E.S.R. and eosinophils were all normal.

Comment.—It may be that the appearance of asthma eleven years ago marked the onset of this patient's present illness and that she is, in fact, an example of pulmonary eosinophilia progressing to florid polyarteritis nodosa (Crofton *et al.*, 1952). The peripheral nerve lesions are of the mononeuritis multiplex variety. According to Heathfield and Williams (1954) this is much less frequently seen in polyarteritis nodosa than a diffuse symmetrical peripheral neuritis. The presence of minimal renal involvement is a very favourable prognostic sign. The spleen is one of the least involved of the major organs (Harris *et al.*, 1939) and such a marked degree of splenomegaly is unusual in this condition. It is interesting that an episode of subarachnoid hæmorrhage occurred when cortisone was temporarily discontinued, but whether this was the result of leakage from a partially healed polyarteritic lesion or rupture of a congenital aneurysm it is not possible to say. Complete remissions have been reported following the use of ACTH (Simpson *et al.*, 1953) and cortisone (McGehee and MacLean, 1954). It is hoped that the dramatic clinical and hæmatological response to cortisone, coupled with the absence of any permanent renal damage, heralds a similarly favourable outcome in this patient.

REFERENCES

Crofton, J. W., Livingstone, J. L., Oswald, N. C., and Roberts, A. T. M. (1952) *Thorax*, **7**, 1.
Harris, A. W., Lynch, G. W., and O'Hare, J. P. (1939) *Arch. intern. Med.*, **63**, 1163.
Heathfield, K. W. G., and Williams, J. R. B. (1954) *Lancet*, ii, 673.
McGehee, E. H., and Maclean, K. (1954) *Brit. med. J.*, i, 1172.
Simpson, J. H., Hall, M., and Morgan, B. (1953) *Brit. med. J.*, ii, 659.

[*May* 11, 1956]

Meeting at Addenbrooke's Hospital, Cambridge

The following Cases and Specimens were shown:

Limb Atrophy.—Mr. B. McN. Truscott.

(1) Multiple Congenital Deformities. (2) Congenital Bowed Tibiæ with Bilateral Pathological Fractures of the Femur.—Mr. T. J. Fairbank.

Palindromic Sarcoidosis.—Dr. L. C. Martin.

Hepatic Cirrhosis.—Dr. N. C. Rothfield (for Dr. D. Gairdner).

Hepar Lobatum.—Dr. B. Black (for Dr. A. P. Dick).

Giant Cell Granuloma Underlying Benign Pigmented Nævus.—Mr. D. A. Cooper (for Dr. Arthur Rook).

Mycosis Fungoides. A Rare Hyperkeratotic Type of Exceptionally Long Duration.—Dr. Arthur Rook and Dr. Danilo Stevanovic.

Acute Porphyria (Two Cases).—Dr. A. S. Cooper (for Dr. A. P. Dick).

Gangrenous Pyoderma in Rheumatoid Arthritis.—Dr. Arthur Rook.

(1) Familial Hæmorrhagic Telangiectasia with Arteriovenous Aneurysms of Lung (Osler-Weber Syndrome). (2) Right Eventration of the Diaphragm Presenting with Cardiac Asthma and Auricular Fibrillation.—Dr. Leslie Cole.

Scleroderma. Extensive Morphœa.—Dr. Arthur Rook and Dr. R. A. Davis.

Intra-epidermal Epithelioma of the Finger.—Mr. D. A. Cooper (for Dr. Arthur Rook).

Diabetes Insipidus.—Dr. B. R. B. Lumb (for Dr. Leslie Cole).

Pure Red Cell Aplastic Anæmia Associated with Pregnancy.—Dr. J. Wedgwood (for Dr. Leslie Cole).

BOOKS RECEIVED FOR REVIEW

Chesser (E.). The sexual, marital and family relationships of the English woman. pp. xxxvi + 642. London: Hutchinson's Medical Publications. 75s. 0d. 1956.

Eton (B.) Clinical report of the Maternity Hospital Cambridge for 1953. pp. 113. Cambridge: United Cambridge Hospitals. 1956.

Hunter (D.), ed. Price's textbook of the practice of medicine. 9th edit. pp. xiv + 1774. Oxford University Press. London: Cumberlege. 63s. 0d. 1956.

Keating (V.). Anæsthetic accidents. The complications of general and regional anæsthesia. pp. vi + 261. London: Lloyd-Luke 25s. 0d. 1956.

Richardson (J. S.), ed. The practice of medicine. pp. vii + 1076. London: Churchill. 40s. 0d. 1956.

Snively (W. D., Jr.), and **Sweeney (M. J.).** Fluid balance for practitioners. pp. xix + 326. Oxford: Blackwell. 51s. 0d. 1956.

Thacker (C. F.). Postural drainage. pp. viii + 56. London: Lloyd-Luke. 8s. 6d. 1956.

Williams (L.). Alcoholism. A manual for students and practitioners. pp. x + 62. Edinburgh and London: Livingstone. 8s. 6d. 1956.

Yoffey (J. M.), and **Courtice (F. C.).** Lymphatics, lymph and lymphoid tissue. 2nd edit. pp. vii + 510. London: Arnold. 60s. 0d. 1956.

BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

Abeloos (M.). La régéneration et les problèmes de la morphogenèse. pp. 253. Paris: Gauthier-Villars. 1932.

Aichhorn (A.). Verwahrloste Jugend: die Psychoanalyse in der Fürsorgeerziehung. pp. 290. Leipzig, Vienna and Zurich: Internationaler Psychoanalytischer Verlag. 1925.

Astruc (A.), and **Giroux (J.).** Les médicaments d'origine biologique. pp. 417. Montpellier: Maloine. 1942.

Baar (V.). Wetter und Krankheiten. pp. 171. Vienna: Ars Medici. 1932.

Barrow (R. L.), and **Fabing (H. D. J.).** Epilepsy and the law: a proposal for legal reform in the light of medical progress. pp. 177. New York: Hoeber. 1956.

Bauer (J.). Die konstitutionelle Disposition zu inneren Krankheiten. 3rd edit. pp. 794. Berlin: Springer. 1924.

Benda (R.). Thérapeutique clinique journalière des affections de l'appareil respiratoire. pp. 164. Paris: Maloine. 1945.

Bleuler (E.). Das autistisch undisziplinierte Denken in der Medizin und seine Uberwindung. 4th edit. pp. 210. Berlin: Springer. 1927.

Brody (C.), ed. Traité d'hélio- et d'actinologie. 2 vols. Paris: Maloine. 1938.

Canlorbe (P.). Le service de santé de la résistance. pp. 204. Paris: Legrand & Bertrand. 1945.

Caullery (M.). Organisme et sexualité. pp. 342. Paris: Doin. 1942.

Chiray (M.), Mollard (H.), and **Maschas (H.).** Syndromes digestifs et pathologie neuro-hormonale. pp. 254. Paris: Maloine. 1944.

Congresses, Rheumatism. IIIe conférence internationale des maladies rhumatismales, Aix-les-Bains, 28 juin–1 juillet, 1956. 2 vols. Chambéry. 1956.

Coria (L.). La pénicilline. pp. 113. Paris: Maloine. 1945.

Dévé (C.). Le travail des verres d'optique de précision. 3rd edit. pp. 540. Paris: Revue d'Optique. 1949.

Douady (D.), and **Meyer (A.).** Manuel de pleuroscopie et de section de brides dans le pneumothorax thérapeutique. pp. 211. Paris: Legrand & Bertrand. 1942.

Duque de Estrada (J.). Obstetricia. Estudios obstétricos de 1897 a 1919. Mexico: Imprenta Murguia. 1955.

[*Continued on p.* 968

Section of Obstetrics and Gynæcology

President—GERTRUDE DEARNLEY, M.D., F.R.C.O.G.

[*May* 25, 1956]

THE following specimens were shown:

Papillary Squamous Cell Carcinoma of the Cervix in Pregnancy.—Mr. R. G. H. HALL.

The case presented as an emergency ante-partum hæmorrhage at 36 weeks' gestation in the fourth pregnancy of a woman aged 28. The patient was extremely fat, weighing 15½ st. and vaginal examination with a speculum was very difficult owing to the vast size of the vagina. A small polyp was seen on the posterior lip of the cervix. The fœtus was lying transversely, and a provisional diagnosis of placenta prævia was made. Examination under anæsthesia was carried out at 37 weeks, in preparation for lower segment Cæsarean section. A friable papillary growth was found on the posterior lip, portions of which were removed digitally for pathological examination, with the possible diagnosis of papilloma of the cervix in pregnancy, or of carcinoma. Histology showed a papillary squamous cell carcinoma of the cervix. Cæsarean Wertheim's operation was performed (Mr. W. G. Mills) and a living male infant was extracted by classical section. Examination of the specimen removed showed that the growth was confined to, but deeply infiltrating the posterior lip of the cervix. There was no involvement of the lymph glands removed.

Mother and baby made good progress after the operation, and the mother discharged herself from hospital on the eleventh post-operative day.

Mixed Mesenchymal Tumour of the Uterus.—Mr. G. W. KORN.

A feature of the case was the coincidental adenocarcinoma of the endometrium, the whole being a true carcinosarcoma. The histiogenesis and lines of treatment were discussed.

Co-existing Hydatidiform Mole and Living Child.—Mr. DAVID BYRON BROWN.

Mrs. J. A., aged 22, was delivered of a living child and a placenta which had undergone hydatidiform changes after 34 weeks of amenorrhœa. She had previously been delivered of one full-term infant and, two years later, a hydatidiform mole.

Less than 20 cases of a viable infant associated with a hydatidiform placenta have been reported. Recurrence of hydatidiform degeneration is rare, its incidence being about 1%.

Mixed Sweat Gland Tumour of the Vulva.—Mr. P. E. HUGHESDON.

Grossly, this presented as a cherry-sized fibroid-like polypoid tumour, dependent from a hymeneal tag at 6 o'clock, in a single woman of 40: it had been present for at least a year. Microscopically, it contained squamous epithelium, sweat gland acini, epithelial trabeculæ, fine reticulate cords, and much smooth muscle. All these showed apparent organic continuity at one or more points, and the tumour was thought to be a myo-epithelioma.

[*June* 22, 1956]

Prolapse of the Umbilical Cord

By PHILIP RHODES, F.R.C.S., M.R.C.O.G.

Senior Registrar, St. Thomas's and Lambeth Hospitals

STILLBIRTH and neonatal death-rates have greatly decreased in the last fifty years. To improve these rates still further will become progressively more difficult as the larger causes of death are overcome. This paper may show that more babies could be saved from the dire consequences of prolapse of the umbilical cord by immediate delivery as soon as the diagnosis has been made. This will entail forceps delivery or breech extraction, if the cervix is fully dilated, and Cæsarean section if the cervix is not fully dilated.

By putting into practice this dictum of "immediate delivery on diagnosis" the results for the fœtus are greatly improved. Cox (1951) doing this had 29 consecutive cases without a fœtal death.

The cases analysed here are from St. Thomas's Hospital and the General Lying-in Hospital, York Road, for the years 1929 to 1955. There are 83 cases in all.

The incidence of prolapsed cord in this series was 1 in 185 deliveries and this may be compared with the figures given by other authors.

Logan (1955) states that in 1950 there were 704,000 "maternities" in England and Wales, i.e. pregnancies of over 28 weeks' duration, and there were also 16,000 stillbirths. If the incidence of prolapse of the cord is taken as 1 in 200 deliveries, which is a fair estimate on the figures given, then this complication occurred about 3,520 times in England and Wales in 1950. Later it will be shown that about half these babies would die, so that it seems

possible that approximately 1,750 babies die annually in England and Wales from prolapse of the cord, and that about 1 in every 16 stillbirths is due to this complication. That this is not an overestimate is shown by Logan's figures in the same article that 6% of the stillbirths in Scotland in 1949 were due to prolapse of the cord. This is an incidence of 1 in 16.

TABLE I.—INCIDENCE

	Deliveries
Group I	1 in 185
Gibberd (1955) ..	1 in 300
Mengert and Longwell (1940) ..	1 in 164
Kurzrock (1932) ..	1 in 169
Cope (1951) ..	1 in 169

TABLE II.—PRESENTATION

Authors	Incidence in each presentation			
	Cephalic	Breech	Shoulder	Face
Mengert and Longwell (1940) ..	1 in 267	1 in 22	1 in 7	—
Kurzrock (1932) ..	1 in 200	1 in 17	1 in 10	—
St. Thomas's	1 in 412	1 in 18	1 in 2	1 in 10

Increasing parity is a predisposing cause of this complication. In this series the incidence in primigravidæ was 1 in 242 deliveries and in multiparæ 1 in 103 deliveries. The incidences in women having their second, third and fourth and subsequent babies were 1 in 168, 1 in 146 and 1 in 44. Baird and Walker (1955) state that 90% of stillbirths in seventh and higher parities are due to malpresentations, prolapse of the cord and precipitate labour.

The effect of *malpresentation* is shown in Table II. It is apparent that prolapse of the cord is about ten times more frequent in breech than in cephalic presentations and that the incidence is still higher in the other two malpresentations.

Other predisposing causes are shown in Table III.

TABLE III.—PREDISPOSING CAUSES

Malpresentation (*see* Table II)	Percentage of cases
Prematurity	25
Disproportion	16
Twins	9
Placenta prævia	5·4
Long cord (75·0 cm. and upwards) ..	
Hydramnios	
Artificial rupture of membranes ..	20

Prematurity, defined by weight, was present in 25% of these cases. Cope (1951) and Kurzrock (1932) give figures of 25% and 29% in their larger series. It is mainly for this reason that the estimate of 1,750 deaths annually previously given has been reduced to 1,000 as this seems a fairer rough estimate of the deaths entirely due to prolapse of the cord.

Disproportion was thought to be present in 16% of these cases. Others give figures ranging from 6·4 to 33%. This wide variation is probably due to the difficulties of diagnosis before the common use of X-rays.

Twins figured in 9% of these cases. Other estimates range from 3·4 to 6·5%. As the incidence of twins is 1·25% of all pregnancies there is a risk of prolapsed cord four to five times greater than in normal labour. The danger is, of course, mainly for the second twin.

Placenta prævia was present in 5·4% of these cases. Others give figures from 3·5 to 5·8%. The risk here is increased because the cord must be carried into the lower uterine segment when the placenta is prævia.

A long cord is a factor which cannot be foreseen. I have had a case in which it was 4 ft. 6 in. long (135 cm.). The usual length of the cord is from 25–75 cm. Of 55 prolapsed cords Mengert and Longwell found the average length to be 73·0 cm. and Cope found the average to be 69·9 cm.

For *hydramnios* I could find no reliable figures, as the diagnosis varies so much with the individual observer. All agree, however, that a sudden gush of liquor can mechanically sweep the cord down and past the presenting part.

Surgical induction of labour had been performed in 20% of these cases. The phrase "artificial rupture of the membranes" in Table III includes induction by Krause's bougies in many cases. I hope this method is no longer used anywhere.

Fenton and D'Esopo (1951) found that artificial rupture of the membranes had been used in 1% of their cases of prolapsed cord, and they use rupture of the forewaters.

Summary.—If the presenting part does not fit fully and snugly into the lower uterine segment, gaps are left through which the cord may pass. Therefore the high head and slack lower segment of the multipara, malpresentations and the other causes mentioned will predispose to prolapse of the cord. The cord will more easily pass through these gaps if it is unduly long or if it is carried down by a flood of liquor.

The fœtal and neonatal mortality rates are high in all series (Table IV). In this group it

TABLE IV.—FŒTAL AND NEONATAL MORTALITY

	%
Group I	52
Mengert and Longwell (1940)	46·6
Kurzrock (1932)	43·9
Cope (1951)	
Cephalic	49·3
Breech	42·5
Transverse	84·3

was 52%. Nearly all authors give a mortality of 50%. Cope (1951) found that the mortality varied with the presentation (*see* Table IV).

Cause of the fœtal mortality.—It is obvious that some babies die of prematurity and that some die of birth injury, usually occasioned by violent attempts at delivery. The rest die of asphyxia. It is usually assumed that the asphyxia is caused by interference with the umbilical blood flow by pressure of the presenting part on the cord. The site of this pressure is stated to be at the pelvic brim, but there are many cases where this cannot be the mechanism. For instance, where the baby lies transversely the presenting part is so irregular or so small that pressure on the cord is most unlikely. Moreover I have had a case where the head was manually held out of the pelvis when the cord was still beating and I was quite sure that there was no direct pressure on the cord, and yet the umbilical circulation stopped and the baby died. It seemed that the likely explanation of this stoppage of the circulation was spasm of the vessels. That spasm may occur can be seen at an exchange transfusion shortly after birth, when on cutting through the cord no blood spurts out. Spasm must also be the explanation of the absence of hæmorrhage from the severed cord in animal births.

Spasm of the vessels may also occur in breech delivery. When the cord is pulled down there may be no pulsation and yet the heart can be still beating. As the cord is being felt on the proximal side of the supposed site of obstruction at the brim, it ought to be able to receive transmitted pulsation. The only reasonable explanation of such occlusion of the vessels is spasm.

Experimental evidence of spasm has been provided by Sir Joseph Barcroft (1951) working on sheep. He wrote "As term approaches, the umbilical vessels become much more likely to resent any sort of manipulation and to show their resentment by contraction" and "The umbilical vessels close on exposure or on any kind of manipulation. Actually the physiology of these vessels is a closed book; they become more and more sensitive as pregnancy proceeds till at term such a simple departure from normal as laying the umbilical cord in air over the edge of a bowl will cause the vessels to constrict". Haselhorst (1929), quoted by Clement Smith (1946), states that if the cord be cut across at birth, bleeding stops in 6–10 pulsations, but this only occurs with the fœtus in air. If the fœtus is in a warmed bath, bleeding carries on much longer. He also showed that if the cord is sponged a focus of spasm is propagated along the cord in both directions. By perfusion experiments he showed that increasing the oxygen content causes contraction of the vessels. This is probably the stimulus which closes the vessels when the normal baby begins to breathe. Thus, I think it probable that umbilical vessel spasm in response to the stimuli of handling or cooling of the prolapsed cord can kill the baby and that this gives a sound physiological reason why immediate delivery on diagnosis should be practised. *The mechanism* by which this spasm is brought about is obscure. One difficulty is that no nerves can be found in the cord, but as far as I know, no one has yet directed attention to the intra-abdominal course of the arteries, to look for nerves and chemoreceptors. One might hope to find a mechanism there similar to that which closes the ductus arteriosus. I wonder, too, if premature closure of the umbilical circulation is responsible for other varieties of unexplained fœtal death, many of which are very obscure.

The clinical significance of this physiology is that methods of therapy which depend on manipulation of the cord or which allow it to cool only help the baby along the road to its death, by functional closure of the vessels.

The diagnosis of prolapsed cord is often obvious. Fœtal distress is an indication for vaginal examination to exclude prolapsed cord.

The treatment of prolapsed cord depends on whether the fœtus is dead or alive and on the dilatation of the cervix. If the baby is dead one should make sure the lie is longitudinal and then let the labour take its course. Absence of pulsation in the cord is no criterion of death, as the heart may still be beating, as I have emphasized in talking of spasm of the umbilical vessels. Cox (1951) delivered 2 babies by Cæsarean section when pulsations in the cord were absent, and both survived. Cope (1951) records a similar case.

If the fœtus is alive and the cervix fully dilated delivery by forceps or breech extraction should be prompt. Table V shows that when this was done 30% of the babies were lost. All other methods showed a loss of 73%.

Before full dilatation of the cervix, by using vaginal delivery we lost 90% of the fœtuses

TABLE V.—TREATMENT AFTER FULL DILATATION OF THE CERVIX

Method	No. of cases		Stillbirths or neonatal deaths	
Expectant	15	30	11	22
Replace and bring down leg	2		2	
Genupectoral position	1		0	
Internal version	5		5	
Internal version and extraction	3		1	
External version	1		1	
Holding up the head. Forceps	1		1	
Leg brought down	1		1	
Tape and catheter	1		0	
Breech extraction	9	20	3	6
Forceps	11		3	

TABLE VI.—TREATMENT BEFORE FULL DILATATION OF THE CERVIX

Method	No. of cases		Stillbirths or neonatal deaths	
Expectant	13	23	13	21
Replacement of cord	2		2	
Internal version	2		1	
Version and extraction	2		2	
Manual dilatation and forceps	4		3	
Cæsarean section	5		0	

(Table VI). The figures are perhaps too small for comparison with Cæsarean section, but other authors by using this policy of immediate delivery have lowered the fœtal loss to about 11%, and from the literature I think the evidence is incontrovertible that the best results for the fœtus in this complication are obtained by Cæsarean section, if the cervix is not fully dilated. When the fœtus survives with other treatment it probably does so by its own resilience and not because of the therapy.

The drawback to the wider use of Cæsarean section for prolapse of the cord is the danger to the mother. The extent of the danger is not easy to assess, but the very best that can be offered may be gleaned from figures given by Marshall (1955). From American sources he found that there were only 4 deaths attributable to the operation in 6,775 consecutive cases. If we can offer this kind of survival to mothers then we can readily advise Cæsarean section for prolapse of the cord to save the baby.

In these days, with all the advances of recent years, mothers expect every infant to survive, and now that obstetrics has been made safe for the mother, our emphasis must shift towards the fœtus. The best chance for the fœtus is provided only by Cæsarean section if the cord prolapses before full dilatation of the cervix. I believe that most mothers will accept the slightly increased risk to themselves for the sake of a live baby.

In domiciliary practice treatment should, as far as possible, be like that in hospital, if the cervix is fully dilated. If the cervix is not fully dilated the patient should be taken to a place where Cæsarean section can be carried out if the fœtus is still alive. First-aid measures are aimed at keeping pressure off the cord, not because this occludes the vessels directly, but because such pressure may cause a focus of spasm as described by Haselhorst. The knee-chest and exaggerated Trendelenburg position may help, but the surest way to elevate the presenting part is manually. Such manual elevation should be kept up till the patient is on the operating table. The cord should meanwhile be kept warm by placing it in the vagina, perhaps wrapped in gauze. Further handling may kill the baby.

Sometimes there may be indication for replacing the cord, wrapped in gauze, above the head and applying a Willett's scalp forceps and sometimes the half breech may be brought down. These would, I think, only apply if the patient was far from hospital.

SUMMARY.—Prolapse of the cord causes *c.* 1,500 deaths annually and is responsible for 1 in 16 stillbirths. Fœtal death may be due to umbilical vessel spasm. Treatment should be by immediate delivery on diagnosis. If conservative treatment has to be used, handling and cooling of the cord should be avoided. I am well aware that I have skated over some of the problems in this complication of labour, in particular those difficulties which arise when the fœtus is premature. I also know that I have given figures which underestimate the maternal dangers of Cæsarean section, but these figures show what is attainable. I hope that by the hypothesis of spasm of the umbilical vessels I have given a reason why, unless immediate delivery is practised, many babies will be unnecessarily lost.

REFERENCES

BAIRD, D. and WALKER, J. (1955) In: British Obstetric Practice. London; p. 868.
BARCROFT, J. (1951) Researches on Prenatal Life. Oxford.
COPE, E. (1951) *J. Obstet. Gynæc. Brit. Emp.*, **58**, 259.
COX, L. W. (1951) *Lancet*, i, 561.
FENTON, A. N., and D'ESOPO, D. A. (1951) *Amer. J. Obstet. Gynec.*, **62**, 52.
GIBBERD, G. F. (1955) A Short Textbook of Midwifery. 6th Edn. London.
HASELHORST, G. (1929) *Ztschr. f. Geburtsh. u. Gynak.*, **95**, 400.
KURZROCK, J. (1932) *Amer. J. Obstet. Gynec.*, **23**, 403.
LOGAN, W. P. D. (1955) British Obstetric Practice. London; p. 1146.
MARSHALL, C. McI. (1955) British Obstetric Practice. London; p. 983.
MENGERT, W. F., and LONGWELL, P. H. (1940) *Amer. J. Obstet. Gynec.*, **40**, 79.
SMITH, C. A. (1946) The Physiology of the Newborn Infant. Springfield, Ill.

Dr. Grantley Dick Read showed a film entitled "Childbirth without fear".

Section of Pædiatrics

President—J. VERNON BRAITHWAITE, M.D., F.R.C.P.

[*May* 3, 1956]

Juvenile Myxœdema Due to Removal of Ectopic Thyroid.—S. B. DIMSON, M.D., M.R.C.P.

P. M., boy, aged 10½ years, was referred when 7 years old because of threadworms and nervous overactivity. The mother remarked on the lump in the mid-line of the neck which had been present for six months. It was the size of a hazelnut and gave the physical signs of a thyroglossal cyst; it was excised in June 1952. However, section showed it to be a colloid adenoma of the thyroid.

At a convalescent home he was noticed to be lethargic with no interest in toys. When seen again in the out-patient department in October, he had become obese, with supraclavicular pads of fat, and was tired and sleepy, unwilling to exert himself, slow in answering questions, and there was a history of anorexia, constipation, and cold hands and feet. He liked sitting in front of a fire. His skin was waxy, pale and dry, with dry, coarse scurfy hair, puffy face with a malar flush, and *erythema ab igne* of the shins. ECG: Rate 84 with low voltage in all leads. Serum cholesterol 286 mg.%. X-ray—pituitary fossa larger than normal; bone age and epiphyses normal. Hb 87%; R.B.C. 4,000,000 with moderate degree of anisocytosis, slight poikilocytosis and hypochromia.

Progress.—He required daily 1½ grains (0·1 gram) of thyroid at first for three to four months but was then stabilized on ¾ grain daily. Radio-iodine uptake (Dr. Stuart Mason): After thyroid treatment was suspended deliberately for one month, in October 1953, "his neck counts showed that there was no significant amount of functioning thyroid tissue". This short interval without thyroid treatment again produced signs of hypothyroidism needing 1½ grains of thyroid for its correction but thereafter his maintenance dose was again ¾ grain a day. He has been a normal boy to date with normal ECG and serum cholesterol.

Past history.—Milestones normal. Tonsils and adenoids removed at 3½ years old.

Family history.—An only child; no thyroid disease in relatives.

Comment.—This case is being demonstrated to show how easy it is to misdiagnose mid-line lumps in the neck unless the thought of ectopic thyroid tissue is uppermost in one's mind. Perhaps the neck should have been palpated more carefully in this case to see whether the tracheal rings were not too easily felt where the normal thyroid gland ought to be and perhaps the so-called cyst should have been aspirated before removal. If doubt had still existed, radio-iodine tests then might have provided the true answer. The literature is, perhaps understandably, reticent about ectopic thyroids in the mid-line of the neck removed in error, except for lingual thyroids which may have to be removed because of obstructive symptoms, but McGirr and Hutchison (1954) described a case almost identical with this one in which a "thyroglossal cyst" was removed with the same unfortunate results. They believe that scanty ectopic tissue, under the intense stimulus of thyrotrophin, eventually enlarges into a recognizable lump and works to the maximum to provide the hormone needs of the body. In our case these needs were fully met as there is no evidence that this boy was short of thyroid; indeed one reason for him being seen in hospital at all in the first place was because his restlessness and overactivity were tiring his mother. An interesting point in treatment of his subsequent myxœdema was that he required twice as much thyroid as the maintenance dose for a period equal to the duration of his deprivation.

One wonders whether, had the lump been left alone, its exhaustion and the spontaneous appearance of myxœdema would in any case have arisen in time. Perhaps, too, there might have been a risk of carcinomatous changes in middle life; Joll (1951) goes so far as to advise removal of ectopic thyroids after the age of 30 for this reason.

REFERENCES

JOLL, C. A. (1951) Diseases of the Thyroid Gland. Ed. F. R. Rundle, 2nd Edn. London.
McGIRR, E. M., and HUTCHISON, J. H. (1954) *Arch. Dis. Childh.*, **29**, 561.

Wolff-Parkinson-White Syndrome.—R. P. BUTT, M.B., B.S. (for S. B. DIMSON, M.D., M.R.C.P.).

I. M., girl, aged 5 years, was found on routine examination to have cardiac enlargement, an apical systolic murmur, and an accentuated reduplicated pulmonary second sound. ECG showed typical Wolff-Parkinson-White complexes with a short P.R. interval and abnormal widening of the Q.R.S. complex.

Comment.—This is a rare syndrome, no cases occurring in 3,400 routine ECGs in infants and children in America (Engle, M. R., 1952, *Amer. J. Dis. Child.*, **6**, 84). It is a developmental abnormality which is usually solitary, but may be associated with other congenital heart lesions. von Tamm, R. H. (1956, *Helv. pædiat. acta*, **1**, 2), states the incidence of associated

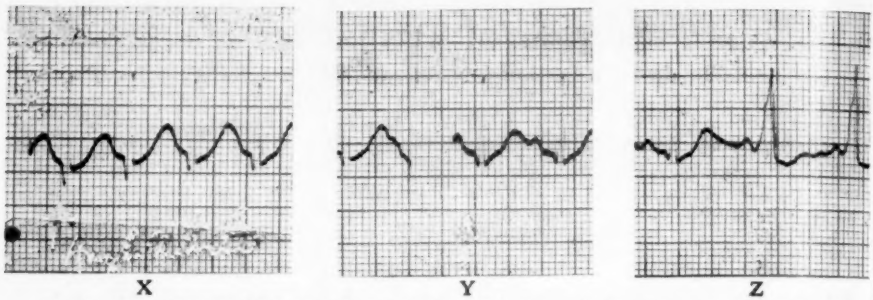


FIG. 1.—ECG after the inhalation of amyl nitrite. This shows: At X normal complexes with sinus tachycardia mimicking paroxysmal tachycardia. At Y gradual slowing of the tachycardia with gradual lengthening of the P.R. interval. At Z abrupt return to abnormal conduction with the presence of Wolff-Parkinson-White complexes.

congenital heart lesions as 11 out of 18 cases. This is higher than in other series. In infants it usually presents as an attack of paroxysmal tachycardia which may occur at any age from birth onwards, and may precipitate cardiac failure and death. There are no other consequences apart from the liability to paroxysmal tachycardia, which occurs in 70% of cases. The ECG complexes are usually normal during the attack and thus it is important to follow these cases in order to demonstrate the Wolff-Parkinson-White syndrome. ECG changes due to underlying cardiac abnormalities only become apparent when those due to the Wolff-Parkinson-White syndrome are absent. Normal complexes can be precipitated by the inhalation of amyl nitrite. In this case there was no underlying abnormality.

Hepatomegaly—Probable Glycogen Storage Disease.—B. W. MEADE, M.D., and T. J. PARKINSON, M.R.C.P. (for Sir CECIL WAKELEY, Bt., K.B.E., C.B., F.R.C.S., and A. DOYNE BELL, F.R.C.P.).

R. M., male, born 26.6.54. Attended out-patients 29.12.55 for an opinion on his distended abdomen. Liver enlarged 2½ in. below costal margin; it was palpable to the left of the midline. The spleen could not be felt. Admitted 12.1.56 on a provisional diagnosis of Von Gierke's disease. He had been a normal full-term baby of healthy parents and grandparents. Sister, aged 4, normal. He had never been overseas.

On examination.—Previous findings confirmed—no abnormalities detected in heart, lungs or nervous system. Height below average. Urine normal; no bile or ketones. Stools usually normal but occasionally loose. Blood count normal; E.S.R. slightly raised (14 mm. in one hour, Wintrobe). Thymol and zinc sulphate flocculation tests normal, as was a thymol turbidity test. W.R. and Kahn negative.

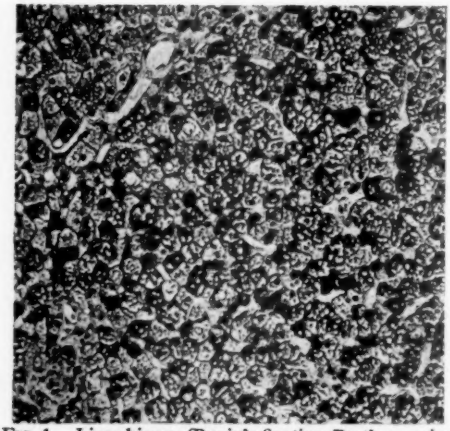


FIG. 1.—Liver biopsy (Bouin's fixative, Best's carmine. ×133).

Adrenaline sensitivity test (17.1.56), using test dose of 0·25 ml. of 1 : 1,000 solution: From a fasting level of 65 mg.% the blood glucose rose to 100 mg.% after 30 min. and at 120 min. had duly fallen to 80 mg.%. Fasting blood glycogen =4 mg.%. Barium meal excluded visceral displacement due to neoplasm. Stool fat was 22 and 14 grams% on two samples; no parasites, cysts or ova seen. Glucose tolerance test: After 20 grams glucose the blood glucose rose from a fasting level of 66 mg.% to 87 mg.% at 60 min., falling to 73 mg.% after 90 min.

Laparotomy (16.2.56). — Under a rapidly induced general anæsthetic the abdomen was opened and the enlargement of the liver confirmed. The organ was slightly pale but appeared of normal texture. A segment was resected for microscopy. The normal size of the spleen was confirmed. No complications post-operatively.

Microscopy of the liver biopsy (Professor H. A. Magnus) showed normal architecture but enlargement of the parenchymatous cells whose nuclei were disposed peripherally. Best's carmine (Fig. 1) and PAS stains showed the presence of an excess of glycogen which was digestible by diastase. Fat stains showed also an excess of fat.

Adrenaline sensitivity test repeated: the blood glucose rose from a fasting level of 70 mg.% to 113 mg.% at 30 min., and fell to 73 mg.% at 120 min.

Despite the persistently negative biochemical evidence we consider that the histological appearances of the liver together with the clinical picture are compatible with the diagnosis of glycogen storage disease.

Dermatomyositis Presenting with Sclerodactyly and Rheumatic Nodules on Tendons.—MARGARET J. COX, M.B., D.C.H. (for J. RUBIE, M.D., M.R.C.P.).

G. P., girl, aged 13 years. Raynaud's phenomenon in hands for two years. Inability fully to extend fingers for one year. Recently general stiffness of body movements and cyanosis of feet when cold. Previous illnesses: chicken-pox, measles only.

On examination there were characteristics of both dermatomyositis and rheumatoid arthritis. The patient had a violaceous complexion and generalized pigmentation of the body. The spleen was just palpable. The hands had smooth skin on fingers, most marked around nail-beds; fine wrinkling of nails; limited extension of fingers; wasting of small muscles; nodular thickenings, like rheumatic nodules, on flexor tendons in palms. Wrist-joint movements were limited. There were no nodules elsewhere.

Wax baths produced no improvement. ACTH produced slight improvement in finger movements and almost complete disappearance of nodules.

REFERENCE.—ANSELL, B. M., and BYWATERS, E. G. L. (1953) *Ann. Rheum. Dis.*, **12**, 283.

"Ileo-colitis" presenting as P.U.O. with Vomiting, Anorexia and Constipation.—M. BRENDA MORRIS, M.D., M.R.C.P. (for S. YUDKIN, Ph.D., M.R.C.P.).

P. H., female, born 4.9.42. Admitted 25.8.54 with three weeks' history of being "off colour" and two weeks' history of vomiting and abdominal pain. She was always constipated.

Past history.—Always constipated. 1952: nausea and abdominal discomfort after food. One attack of acute abdominal pain. Non-urgent appendicectomy July 1953 at another hospital. Appendix mildly inflamed, no other abnormality noted; symptoms relieved.

On examination.—Noticeably thin, but no other abnormalities found.

Investigations.—E.S.R. 55 mm. in one hour (Westergren). Blood count: Hb 74%; film slightly hypochromic; W.B.C. 8,000, differential normal. Other investigations including blood and stool culture and fæcal occult blood persistently negative.

Progress.—For eight weeks she had an irregular fever up to 101° F., had anorexia and vomited irregularly. Stools were very constipated except for the occasional passage of a single softer offensive stool.

Chloromycetin was then given empirically and produced a dramatic symptomatic improvement with normal temperature and fall in E.S.R. to 15 mm. She relapsed after Chloromycetin was discontinued but further clinical remission followed a second course of Chloromycetin and was sustained for some weeks. She was discharged to out-patients.

By March 1955 she had again relapsed with recurrence of fever, anorexia and vomiting and raised E.S.R. She was readmitted to hospital. Constipated stools were passed as infrequently as once a week, but the constipated results following enemata were sometimes offensive.

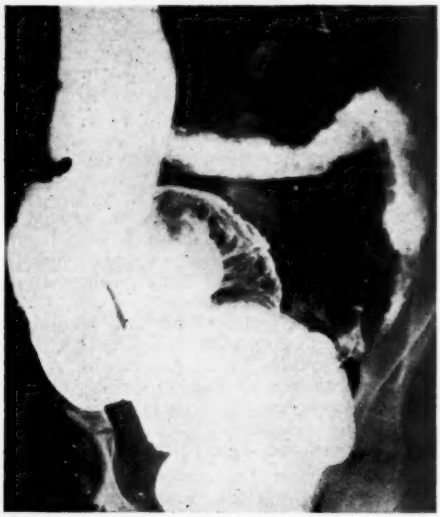
Barium meal and follow-through, March 1955 (Dr. G. Osborne), showed no abnormality.

Symptoms and fever continued until June 1955 when pus cells were found in a single stool for the first time. Sulphasuxidine was given with considerable clinical improvement. Stools, however, became looser and offensive, but were never passed more than once a day. She remained on Sulphasuxidine for six weeks, during which (July 1955) she developed erythema nodosum and a painless localized area of conjunctival injection of the right eye. These cleared up in a few weeks. The stools now became more frequent, up to three a day, dark and offensive, but not very loose. Vomiting, anorexia and fever recurred and the E.S.R. was 47 mm. in one hour. Hb 79%.

Barium enema, July 1955 (Dr. G. Osborne), showed a "polypoid" appearance of the colon extending from the cæcum to the splenic flexure. The mucosal pattern of the descending colon was normal (Figs. 1 and 2).

Sigmoidoscopy (Mr. W. W. Davey).—Fæces semi-fluid. Mucosa normal.

Treatment.—Blood transfusion and Imferon followed by cortisone for six weeks. Oral penicillin and streptomycin ten weeks. Improvement was dramatic. E.S.R. fell to 11 mm. in one hour. She gained weight and became symptom free. A formed stool was passed twice daily. She returned to school and was perfectly well until March 1956 when mild nausea and vomiting recurred. Oral penicillin and streptomycin were again given for four weeks with complete remission of symptoms. Stools were normal on microscopy and culture, but E.S.R. was 35 mm. in one hour.



L FIG. 1. R

R FIG. 2. L

FIG. 1 (26.7.55).—Shows "polypoidal" mucosal pattern of ascending and transverse colon.
FIG. 2 (12.8.55).—Shows normal mucosal pattern of descending colon.

R L

FIG. 3 (9.4.56).—Shows "polypoid" mucosal pattern of transverse colon and proximal part of descending colon.

Barium enema, April 1956 (Dr. G. Osborne), now showed dilatation of the terminal ileum with "polypoid" mucosal pattern. The "polypoid" appearance involved the ascending and transverse colon as before and appeared now to have extended into the proximal part of the descending colon (Fig. 3).

In spite of her almost complete clinical remission, not only was there no evidence of healing of the colonic lesion on X-ray, but there was also apparent extension of the lesion into the descending colon, and definite involvement of the ileum. After much deliberation it was decided that a total colectomy should be performed while it was still possible to perform an anastomotic operation. It was felt that further delay might ultimately necessitate a permanent ileostomy, a procedure to be avoided in one so young.

Operation, 26.7.56 (Mr. W. W. Davey).—Total colectomy and excision of 10 cm. of terminal ileum with ileo-rectal anastomosis. At operation there was found enlargement of the mesenteric glands draining the affected part of the colon and loss of ileocæcal angle. Macroscopic changes involved about 10 cm. of the terminal ileum and extended to the splenic flexure.

Histology (Dr. B. C. Morson, St. Mark's Hospital).—The affected terminal ileum and colon show extensive longitudinal ulceration with coarsely nodular or cobblestone appearance of the intervening mucosa. There is a sharply demarcated junction between abnormal and normal mucosa in the region of the splenic flexure.

Sections of the terminal ileum, cæcum, ascending and transverse colon show extensive areas of mucosal ulceration with lymphoid overgrowth and foci of epithelioid cells and giant cells. The regional lymphatic glands also contain many giant cell systems. No caseation or tubercle bacilli seen. The descending and sigmoid colon show only a few scattered and very small areas of mucosal ulceration.

POSTCRIPT (1.10.56).—*Final diagnosis.*—Crohn's disease of the terminal ileum and right half of the colon. The child has had an uninterrupted post-operative course and is now back at school. Her E.S.R. is 12 mm./first hour (Westergren). She feels and looks well and has two stools normal or slightly relaxed each day.—M.B.M.

Section of Proctology

President—HAROLD DODD, Ch.M., F.R.C.S.

[*May* 2, 1956]

DISCUSSION ON ILEOSTOMY

Dr. Neil W. Swinton (Department of Surgery, The Lahey Clinic, Boston, Massachusetts):

The Management of Ileostomies

In the light of our present knowledge it is generally accepted that total colectomy with a permanent ileostomy is the only method of cure for the patient with chronic non-specific ulcerative colitis (Zetzel, 1954).

The frequency and seriousness of the complications which have been associated with ileostomy in the past, however, have militated against the general acceptance of this principle both by many in the profession and by patients. This has resulted too often, for many with this disease, in delay of surgical intervention until well beyond the optimal time for such treatment, with resulting serious complications and high mortality.

The purpose of this presentation is to review briefly our overall experience at the clinic with the surgical treatment of chronic ulcerative colitis (Cattell and Colcock, 1955*a*, *b*), to discuss some of the more general problems that have been presented by patients left with a permanent ileostomy and to review in detail the complications encountered following an ileostomy and the methods employed to prevent them. We believe that a high percentage of these patients, even though left with a permanent ileostomy, can be returned to health and to a well adjusted position in society.

In the twenty-five-year period from 1928 to 1952 inclusive, 871 patients with chronic ulcerative colitis were seen at the clinic. Of this number, 413, or 47%, had 858 surgical procedures. The percentage of our patients submitted to surgical treatment is higher than the 15 to 25% usually quoted (Zetzel, 1954). This is due in part to the numbers of patients referred to us primarily for surgical treatment after they have had extensive medical treatment elsewhere. We have, however, advocated for many years that a high percentage of these patients be submitted to colectomy as the only means of obtaining a permanent cure in this disease.

Once an ileostomy has been performed for chronic ulcerative colitis, almost always it must be followed by total colectomy. Colcock and Mathiesen have made a detailed analysis of 307 patients from our group who had ileostomy and colectomy between 1946 and 1954 (Colcock and Mathiesen, 1956). In 12 of this group intestinal continuity was restored; 5 of the 12 patients had an ileostomy for disease which seemed to be limited to the right colon. Of these 5, 2 have been well for two and three years respectively. Of the remaining 7 in whom the disease seemed to be localized elsewhere than the right colon, 2 have shown no further evidence of colitis for three years, but in the group of 12, 8 have ultimately required permanent ileostomy and colectomy for recurrent or persistent disease.

In any evaluation of the surgical treatment of a disease, both the immediate and late mortality must be considered. In 1954, Rogers, Bargen and Black of the Mayo Clinic reported a disturbing mortality in a series of 124 patients with ileal stomas who had been operated on between 1940 and 1949 (Rogers and Bargen, 1953; Rogers *et al.*, 1954). They stated that by 1952, 46% of these patients were dead. The hospital mortality had been 23·4% and an additional 21 patients had died after leaving the hospital, 8 of whom had had metastatic malignant disease. Only 14% of their series had lived for over one year without some serious complication. These figures can be explained by the fact that only 5% of all patients seen by them with chronic ulcerative colitis were surgically treated, an indication that only the most desperately ill patients were operated on.

In Colcock and Mathiesen's series from this clinic of 307 patients the immediate operative mortality was 3·8%; these 11 patients died in the hospital from all causes following ileostomy alone or with colectomy. Up to the present time 23 additional patients have died from all causes. This can be considered an absolute patient mortality of 11·1%.

There is little to be added concerning the incidence of cancer in chronic ulcerative colitis. In this series being discussed, cancer developed in 11 patients, an incidence of 3·5%. In 9, carcinoma developed in the colon remaining after ileostomy; in the remaining 2, the carcinoma was unsuspected and found in the surgically removed specimen.

Pregnancy is an important problem to the patient who has had a colectomy and permanent ileostomy. 10 patients in our series became pregnant after ileostomy; 5 of the 10 had normal deliveries through the birth canal at or near term. 2 suffered acute exacerbations of the ulcerative colitis, 1 of whom had a spontaneous abortion. 2 patients required a

therapeutic abortion and 1 patient died of eclampsia at term. In all 5 patients who did not have a normal delivery, part or all of the colon remained. For this reason we do not advise patients to undergo pregnancy until all of their colon has been removed.

The occurrence of regional ileitis in patients with chronic ulcerative colitis can be a most serious complication. In our group extensive regional ileitis developed in 10 patients requiring operative intervention in addition to the ileostomy and colectomy. In 5 of the 10, the regional ileitis followed the chronic ulcerative colitis, in 4 it appeared to be coexistent, and in 1 the chronic ulcerative colitis occurred six years after the small bowel had been resected for ileitis. In one of our patients the process involved successively the colon, the small bowel and stomach, and in another the œsophagus was involved. We do not believe that it is finally proved whether or not these two conditions are distinct entities. From a pathological standpoint there is some reason to believe that they are, but from a clinical standpoint it is to be noted that they frequently coexist, and, when they do, they present an exceedingly difficult problem from the standpoint of surgical management.

Skin irritation surrounding an ileal stoma can be very distressing. In Colcock and Mathiesen's series of 307 patients, some appreciable degree of skin irritation developed in 49, or 15·9%. In 12 it occurred while the patients were in the hospital and in the remainder it followed their hospital discharge. We believe that if these patients have a well-constructed stoma and a properly fitting, watertight, adherent apparatus applied at the time of operation and continued indefinitely, the problem of skin irritation will be minimal.

Some degree of small bowel obstruction is generally recognized to be and in our experience has been the most frequent complication following colectomy and ileostomy. Warren and McKittrick (1951) have published an excellent discussion of this subject and have emphasized the term "ileal dysfunction". The loss of large amounts of fluids and resulting electrolyte imbalance caused by small bowel obstruction can be the most serious complication with which we have to deal. In our series, 134 patients, or 43·6%, developed some degree of small bowel obstruction following surgical treatment. In 62 of the 134 it was temporary and relieved by non-operative measures. In 58 of the 72 who required surgical intervention, the obstruction developed after the patient's discharge from the hospital. That considerable progress has been made in eliminating this complication is illustrated by the fact that in 1946, the first year of this study, there were 15 instances of small bowel obstruction. In 1954, intestinal obstruction occurred in only 2 patients, in 1 of whom surgical treatment was required. The problem of fluid loss and electrolyte imbalance has been ably discussed by Wilson (1955). In our series this was a prominent complication in 12% (37 cases), in 40% of whom the complication developed after the patients left the hospital. This fact emphasizes the point that these patients must be carefully instructed in the necessity for immediate treatment if abnormal amounts of fluid are being lost from their intestinal tract at any time. Many technical factors have been developed that have resulted in greatly diminishing this incidence of obstruction. The use and development of appliances that can be placed over the ileal stoma at the time of operation; the absence of draining tubes in the small bowel; the construction of stomas designed to avoid stricture formation at the skin level; the proper intra-abdominal fixation of the terminal ileum; the obliteration of the right gutter, and the reperitonization of raw surfaces so as to avoid adhesions have all been important technical developments.

A fistula developed, usually at or above the skin margin of the ileostomy, in 68, or 22%, of our series. These occur almost always as a result of an ill-fitting appliance or the formation of a band of scar tissue at the junction of skin and ileum, or both.

Prolapse of the protruding ileum has been a distressing complication in the past. Warren and McKittrick reported an incidence of 13% (27 cases) in their series of 210 ileostomies, and Brooke (1952, 1954), 2 in 37 patients. In our series only 1 patient has had this complication during the past five years.

The ileal stoma may retract, and this complication occurred in 11 cases or 3·5% of our group, but in only 2 instances since 1951. If the ileum retracts to the level of the skin, surgical revision will usually be necessary to permit the watertight attachment of an ileostomy bag.

A post-operative herniation at the site of the ileostomy occurred in 13 (4·2%) of our series, but was not noted in any of the 53 patients of our group operated on during the last two years. We do not believe that any of these complications will occur if a proper ileostomy is made, adequate care is taken with the closure of the abdominal incision and the ileum is properly fixed within the peritoneal cavity.

There has been some discussion as to whether an ileal stoma should be made through the initial abdominal incision or through a separate stab wound. In our series the ileal stoma was made in 262 of the cases through the primary abdominal incision and in 45 through a separate stab wound. Theoretically it would seem that an ileostomy appliance might fit more securely and be more satisfactory if it were made through a separate stab wound where

a circular segment of skin had been removed. In our series the incidence of skin irritation in those patients having a stab-wound ileostomy was about one-half that associated with ileostomy formed in the laparotomy incision. The incidence of obstruction with a stab-wound ileostomy, however, was somewhat greater than when the small bowel had been brought out through the primary incision. The incidence of fistula, prolapse and retraction was essentially the same in both groups. If the primary incision was properly constructed, whether the ileostomy was brought out through the stab wound or through a primary incision did not seem to be too significant. At the present time, however, the majority of our ileostomies are being made through a separate stab wound.

To us, a most important and distressing complication observed in our patients has been the stricture formation resulting from the scar and granulation tissue at the junction of the ileum and skin following the formation of an ileostomy (Fig. 1). This can be very troublesome

FIG. 1.—Band of constricting scar at junction of mucosa and skin, the cause of so many of the complications associated with ileostomy.

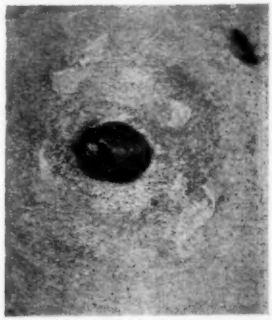


FIG. 3.—Absence of scar contracture resulting from primary healing of mucosa and skin. Technique of mucosal graft advocated by Turnbull.

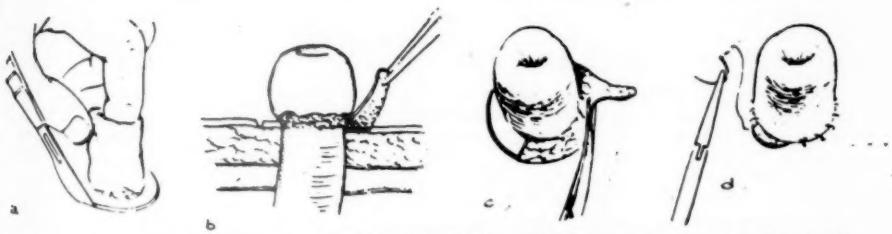


FIG. 2.—A technique of excision of constricting band of scar with suture of mucosa to skin margin. [Adapted from Warren and McKittrick (1951).]

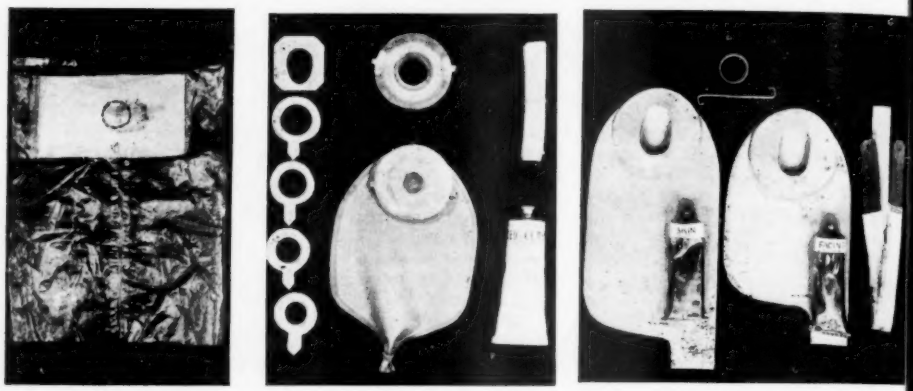
and has been responsible for a high percentage of the complications that have been seen in the past in so many of these patients. Following Patey's (1951; Annotations, 1954) original suggestion of everting and suturing mucosa to skin in colostomies to prevent stricture formation, progress in this regard has been made by Brooke (1954) in England and Turnbull (1953, 1956) in America—a technical procedure which has every indication of further reducing the incidence of stricture formation following ileostomy (Fig. 2).

Rupert Turnbull of the Cleveland Clinic, in a report being published later this year, presents a series of 50 consecutive patients on whom he has used a newly developed type of mucosal graft. This technique will be well illustrated in his publication. It consists of drawing out the terminal ileum at least 2 in. through the abdominal wall, excising the distal one-half of the serosa from this stump and turning back, as a mucosal graft, the mucosal and submucosal structures, suturing this everted mucosa to the adjacent skin. This method allows primary healing between these two surfaces and prevents the introduction of infection with the resulting granulation tissue and constricting scar, so commonly observed (Fig. 3). In his series to date, 5 patients have required additional surgical treatment, an incidence of 10%. In 3 of these 5 patients a mild degree of skin stricture developed which was excised locally, and in 2, reconstruction of the ileostomy was required, 1 by an intra-abdominal and 1 by an external approach.

We have had a more limited experience with this procedure but within the past year we

have employed it in 20 such cases, without any complications to date. It seems to us to be a distinct technical advance in the construction of a permanent ileostomy.

One of the most important contributions in recent years toward the complete rehabilitation of patients with ileostomies has been by lay groups, the so-called QT clubs (Linneberg, 1954). The name QT had its origin in the Q and T wards of Mount Sinai Hospital in New York where this idea was first developed. The group in Boston was formed around a nucleus of 9 women who first met in 1952. At the present time this group meets monthly in one of the Boston hotels. Membership is open to both sexes and the meetings are alternately open and closed. The assistance which these clubs have given, not only to the profession and to appliance manufacturers but primarily to patients, cannot be overemphasized. In a large measure they have repeatedly been responsible for the complete readjustment of our patients.



A B C

FIG. 4.—Types of appliances for ileostomies. A, Inexpensive plastic bag attached to abdominal wall with double-faced adhesive. Very satisfactory for immediate post-operative and temporary hospital use. B, Type of apparatus useful during stage when ileostomy is contracting because of adjustable fittings. C, Example of form-fitting ileostomy bag for permanent use.

At meetings of these clubs almost invariably equipment is displayed. Talks are given by members of the group, by appliance manufacturers and by the profession. These talks may concern cements, adhesives, deodorants, methods of cleansing, the changing of appliances, the wearing of a belt, night-time problems, girdles, clothing and various other subjects. The members of these clubs emphasize that their most important technical complication has been that of skin irritation. They believe that this almost invariably is due to an improperly fitting appliance or to sensitivity to a cement or an adhesive. They have a simple skin-testing device which is circulated without cost among their members and which has been of great assistance in this regard. These clubs maintain a special visiting committee whose function it is to visit both pre-operative and post-operative patients in the hospitals. These visiting committees have been of inestimable value in many of our more serious situations. The club members maintain a close liaison with appliance manufacturers, and not only develop and pass on to such manufacturers new ideas which have originated among their members, but experimentally try out new products. They publish a monthly bulletin which originally was issued only to their group but more recently has been circulated to a large number of physicians and appliance concerns. They have intentionally not admitted patients with colostomies to their organization.

I have been informed that there has been considerable discussion recently in London on the feasibility of anastomosing the ileum to the rectum and eliminating the ileostomy in the surgical treatment of patients with chronic ulcerative colitis. At the clinic we have had no experience with this operation. The reports of Ravitch, Wangensteen, Best (1952), Devine, Schneider (1955) and others on this subject are well known. Best, in 1952, reported a collective series of 29 cases in which he thought the results had been satisfactory in one-half. Corbett (1954) reported 12 such cases, in 8 of which a good result had been obtained. In our experience the high percentage of our patients with chronic ulcerative colitis and serious anorectal complications has discouraged us from attempting this procedure. Stricture of the rectum with multiple fistulas, abscesses and incontinence, usually the result of previous inadvisable surgery, has presented problems which to us in the past have not seemed to be compatible with preservation of the rectum. Also, our increasing realization of the frequency

of malignant degeneration in such retained segments of bowel has seemed an additional factor weighing against this attitude.

Another technique which was first described by Dragstedt in 1941 has been that of the skin grafting of the ileal stoma. This method has, perhaps, reduced the incidence of stricture formation and skin irritation, but again it has not seemed to us to be applicable for many patients. Bargen, in 1954, reported 30 such cases at the Mayo Clinic, and Black and Sholl (1954) stated that the end-results seemed to be satisfactory in 75% of them.

In conclusion, at the clinic at the present time we believe that with the technical advances that have been made in the formation of the ileal stoma, with the development of watertight adhesive appliances (Fig. 4), the reduction in operative mortality, and the help that is available for the social readjustment of these patients through lay groups such as the QT clubs, the vast majority of patients who have had an ileostomy and colectomy can be satisfactorily returned to a useful, well adjusted and healthy, happy place in society.

We recognize that colectomy and permanent ileostomy may not be the ideal approach to this disease. It is hoped that some day in the future, with further basic studies on the ætiology of this condition and improved medical measures, this disease can be either controlled medically or prevented in almost all cases. But in view of our present knowledge, colectomy and ileostomy is not incompatible with a relatively normal existence, and patients should not be discouraged in undergoing such treatment when it is definitely indicated.

REFERENCES

Annotations (1954) *Lancet*, ii, 1317.
Best, R. R. (1952) *J. Amer. med. Ass.*, **150,** 637.
Black, B. M., and Sholl, P. R. (1954) *Arch. Surg., Chicago*, **68,** 454.
Brooke, B. N. (1952) *Lancet*, ii, 102.
—— (1954) *Postgrad. med. J.* **30,** 237.
Cattell, R. B., and Colcock, B. P. (1955*a*) *Postgrad. Med.*, **17,** 114.
——, —— (1955*b*) *Surg. Clin. N. Amer.*, **35,** 817.
Colcock, B. P., and Mathiesen, W. L. (1956) *Arch. Surg. Chicago*, **72,** 399.
Corbett, R. S. (1954) *Postgrad. med. J.*, **30,** 232.
Linneberg, E. (1954) *New Engl. J. Med.*, **251,** 1008.
Patey, D. H. (1951) *Proc. R. Soc. Med.*, **44,** 423.
Rogers, A. G., and Bargen, J. A. (1953) *J. Amer. med. Ass.*, **151,** 815.
——, ——, and Black, B. M. (1954) *Gastroenterology*, **27,** 383.
Schneider, S. (1955) *Arch. Surg., Chicago*, **70,** 539.
Turnbull, R. B., Jr. (1953) *Amer. J. Surg.*, **86,** 617.
—— (1956) Personal communication.
Warren, R., and McKittrick, L. S. (1951) *Surg. Gynec. Obstet.*, **93,** 555.
Wilson, A. O. (1955) *Postgrad. med. J.*, **31,** 289.
Zetzel, L. (1954) *New Engl. J. Med.*, **251,** 610, 653.

Mr. Bryan N. Brooke (Surgeon, United Birmingham Hospitals):

Though ileostomy as a technical procedure is difficult to dissociate from colectomy and pan-proctocolectomy, it is the ileal stoma that calls for all the care and attention if surgery for ulcerative colitis is to have a successful outcome. If the ileostomy fails all else fails, for the adherent bag, which has revolutionized the surgical treatment of this disease, cannot then do its work of collecting semi-fluid fæces cleanly, without leak and without skin excoriation.

Unfortunately, memories of the days before the advent of the adherent bag die hard so that, to many, the term ileostomy still conjures up a leaking incapacitating disaster. Professor T. L. Hardy was, I believe, with Mr. Rodney Maingot, one of the first to introduce the bag into this country; so through my association with him, all the operations I have performed have been designed to provide a stoma around which the bag may be attached.

Of 131 patients operated on up to December 1955 all have received my surgical attention. Since 5 patients were subjected to laparotomy only, there were 126 patients who were treated with elective surgery, 9 of whom had simple resection and end-to-end ileo-sigmoid or ileo-rectal anastomosis (3 of these later required conversion to permanent ileostomy). Thus 117 patients were submitted to the routine of ileostomy and excision. There have been 11 operative deaths and 4 late deaths. 101 of the ileostomy survivors have been followed to December 1955, 92 of them by questionnaire. Of these 101, 39 had their ileostomy established 5 or more years ago, 25 between 3—5 years and 37 up to three years. 90 out of the 101 patients were quite fit; 10 stated they were in reasonable health, 7 still being convalescent from a primary or subsequent operation; and one regarded himself as being unfit for other reasons than ulcerative colitis and its treatment. All patients other than the 7 who were still convalescent were at full work with the exception of 2 who were practically blind as a result of eye complications. 96 patients regard their ileostomies as satisfactory; the remaining 5 patients who do not consider their ileostomies as satisfactory, due either to occasional leakage or excoriation, are nevertheless able to do full work. 2 patients have had babies, and breast fed them; another is pregnant.

It has been a long and even tedious path, not without its disasters. There have been 221 operations with 11 deaths, an operative mortality of 5%, a patient operative mortality of 9%. 4 late deaths have occurred, 2 from obstruction, 1 from carcinoma and 1 from lung abscess; so that the overall patient mortality has been 12%.

The problems we have encountered fall into two groups, the complications and the imponderables—those things that at first were unknown to us. The complications fall naturally into two groups: the first is intestinal obstruction. Apart from obstructive episodes of colic lasting twelve to twenty-four hours, which occur in approximately one-fifth of patients within a week of the institution of an ileostomy and which correct themselves, obstruction has been a late event calling for readmission and laparotomy for its relief in 6 patients, 5 due to adhesions and 1 to intussusception—a rare complication. In addition, there have been the two late deaths already referred to from this complication. One further patient in the ileoproctostomy group also developed obstruction.

The second group of complications are those which render the ileal stoma inefficient. In the technique of ileostomy the simple expedient of exteriorizing the ileum and allowing the mucosa gradually to cover the serosa did not satisfy me since the granulation tissue which formed over the serosa led to fibrosis and stenosis in a quarter of my patients. In 1951 I therefore tried eversion and immediate suture of mucosa to skin. This is different from and simpler than the technique of Turnbull and Crile who remove muscle and serosa from the portion which is to be everted. Stenosis has virtually been eliminated thereby and a flexible stoma is formed which drops neatly into the bag thus reducing skin contamination; some patients have even found that they need not use the adhesive glue. On 106 patients I performed the original ileostomy; 11 with pre-existing ileostomy came to me because they required excision of the bowel. Table I gives the complications and their frequency.

TABLE I

Ileostomy	42	106	
Primary colectomy	49	(11 of 117 patients had pre-existing ileostomy)	
Primary pan-proctocolectomy	15		

COMPLICATIONS	
Prolapse	3
Recession ..	6
Fistula	3
Stenosis	9/35+1/71
Operative revision	9+4 (10+1)
Rubber-sensitive	2

Prolapse and recession are due to the same primary cause, namely, a failure to fix or a subsequent detachment of the mesentery in the para-ileal gutter. Cure for both calls for laparotomy and reattachment of the mesentery to the parietes. When performing a second stage for the excision of the bowel I find it advisable to examine the para-ileal gutter since in a number of cases the mesentery becomes detached during the interval between the first and second operations, perhaps due to increase of weight and deposition of fat within the abdominal wall and mesentery causing the latter to pull away. Fistula is always to be found inferiorly and in my experience is due to placing the stoma too low so that the flange of the bag impinges on the thigh when the hip is flexed; the flange is then pushed against the ileostomy and chafes it. In the first 35 ileostomies I performed there were 9 cases of stenosis and in the subsequent 71, in all of which eversion had been undertaken initially, there has been only one case of stenosis. All these complications have led to revision in 9 cases at the time of a subsequent operation for excision and in 4 at an operation specially undertaken for revision alone. The figures in brackets under "operative revision" in Table I refer to the 11 patients who came to me with pre-existing ileostomies; all of them required revision, 10 being undertaken at the time of a further stage of excision: in some of these cases the ileostomy was revised in order to fit the adherent bag. These figures for operative revision are in complete contrast to those of the Mayo Clinic given recently by Bargen who states that only 14% of 124 patients were free of complications at the stoma within one year and about 43% of those surviving one year required an operation for revision. Perhaps these figures are an indictment of the skin-grafting technique, which has never found favour in this country.

The first of the problems we encountered is no longer an imponderable. It concerns colo-ileitis. Ileostomy can be performed after the ileum has become involved due to the breakdown and incompetence of the ileo-cæcal valve. In this I assume the distinction between colo-ileitis and entero-colitis (or what is called right-sided colitis in America and by some here). The valve has been incompetent in 26 patients, with ileitis in 15, none of whom had steatorrhœa. I have made the stoma through inflamed ileum in most of these patients so as not to sacrifice more small bowel than necessary. The ileitis has subsided in all, though I must report that in one patient, who died from a late obstruction, ileitis was present at autopsy due, probably, to the late obstruction. All the others survived (7 over three years) without trouble, their stomata, which started existence granular and inflamed, now being normal. In my experience patients with ileitis are in the most emaciated group but nevertheless stand operation well.

The other imponderable concerns chemistry and is not yet fully solved. What comes out of an ileostomy? Nitrogen loss at the outset is 3 grams at the most daily to 1–2 grams in the established ileostomy—much less than is lost in the stools before ileostomy. Sodium is lost in direct proportion to the volume of fluid from the ileostomy, initially at the rate of 200–300 mEq./litre—about twice the concentration in tissue fluid; in an established ileostomy this appears to fall to 125–150. If we know the volume output from the ileostomy we can assess how much Na to give a patient to avoid Na depletion arising in the early days when the output is anything up to 3 litres in twenty-four hours. K is capricious and sometimes comes out in large quantities. The amount of K needed for repletion can only be estimated by assessing the amount lost from the proportion in aliquots of twenty-four-hour collections of urine and ileostomy exudates. Ca output may prove to be an exciting story physiologically which I have no time to consider now; suffice it to say that the established ileostomy puts out up to 2 grams of Ca daily (Fig. 1).

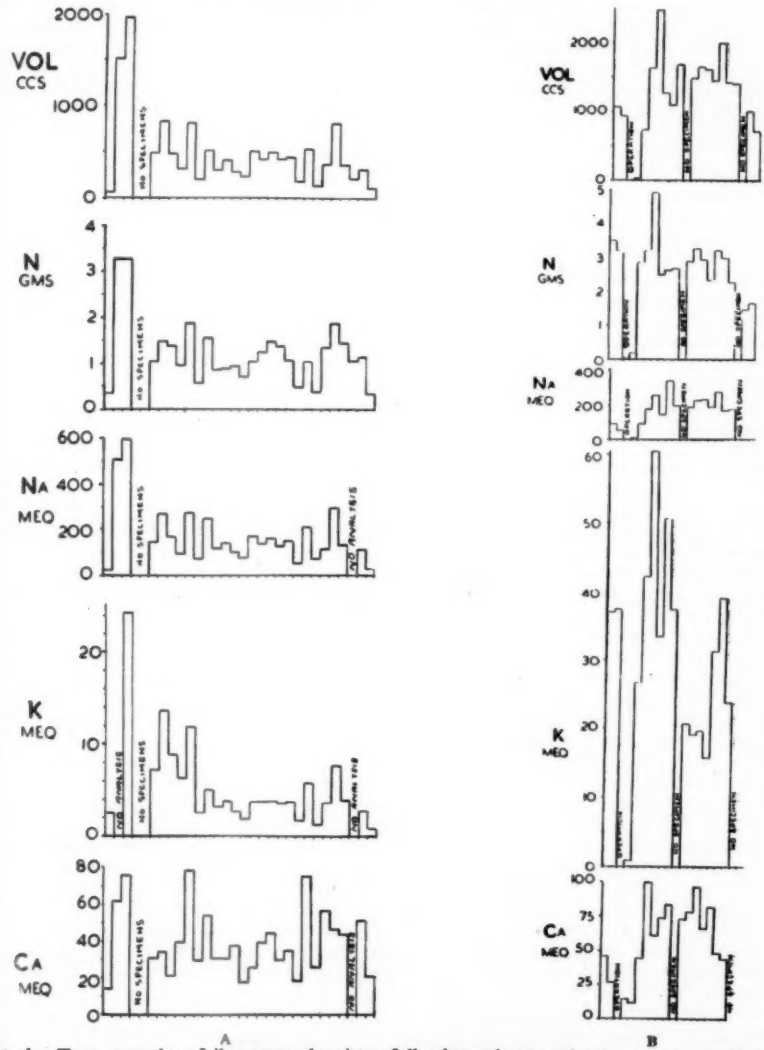


FIG. 1.—Two examples of ileostomy chemistry following primary colectomy. A, represents the usual findings; in B an abnormally high potassium output was noted with an apparent compensation in sodium output. The histograms represent volume, nitrogen, sodium, potassium and calcium output per diem.

An ileostomy association has been started by patients in the Midlands; it is in touch with QT Boston. We hope the St. Mark's group to be inaugurated shortly will link up with it.

I do not regard ileoproctostomy as a routine procedure for ulcerative colitis. There are certain limited indications; in children who cannot be expected to manage an ileostomy it must be undertaken with a view to maintaining reasonable health until they are of an age when an ileostomy is feasible; for the same reason a permanent ileostomy is not suitable for patients with mental deterioration. Resection may also be appropriate for those patients with limited areas of disease or with a rectum that is not seriously damaged and with no anal lesions—but this is rare; nevertheless I have had to unpick the anastomosis and institute a permanent ileostomy in 3 patients in this category. The reason why resection and anastomosis cannot be regarded as routine is because serious complications may arise for the first time when the rectum alone remains, as after anastomosis; and I have seen severe arthritis start under these conditions. Furthermore, perforation in and severe hæmorrhage from the rectum can obviously not be treated by any means other than excision.

Even after deflection of the fæcal stream via an ileostomy the rectum does not appear to heal. Dr. George Lumb of the Gordon Hospital has been kind enough to examine and report on 10 specimens of the rectum which I have removed at a second stage from anything between one to seven years after the original ileostomy. In all the disease persisted despite rest in the physiological sense.

REFERENCES

BARGEN, J. A. (1956) *Gastroenterology*, **30**, 316.
TURNBULL, R. B., and CRILE, G. (1955) *J. Amer. med. Ass.*, **158**, 32.

Mr. Stanley Aylett (The Westminster Hospital Teaching Group, Gordon Hospital):

The Avoidance of an Ileostomy by Ileo-rectal Anastomosis

However much we may be able to overcome the disabilities attendant upon an ileostomy by the perfection of the technique of its formation and by the improvement of bag design it still remains a frightening burden with which to saddle a patient for the rest of his life. Particularly is this true when, as so often is the case, the patient is at the threshold of his early adult and married life. Moreover an ileostomy is oftentimes not the end of his troubles as the complications associated therewith are by no means inconsiderable.

I feel that surgical opinion has advanced too far in its present advocacy of total ablation of the large intestine and the formation of an ileostomy as the elective treatment of the condition without a preliminary and determined effort to explore every possibility of achieving a more conservative solution of the problem. I hope to be able to show that in order to return the patient to normal good health the removal of the rectum is not necessary save in the most rare case, and that it may be retained and anastomosed to the ileum so that the normal channel of evacuation is restored.

Surely the extent of any surgery should be limited to that necessary for the return to good health. Even though the remnant of bowel that we leave behind is not absolutely normal in structure does it really matter—if it produces no symptoms, if the patient can follow every economic and social pursuit that he previously followed, if he puts on weight measured often in stones rather than pounds and if the few extra bowel actions that are inevitable after the removal of the colon worry him or her not a jot? We do not in other fields of surgery remove an organ that may be slightly abnormal but which is not producing any symptoms. There are many who will deny that where continuity is restored a return to good health is possible, but such has not been my experience, nor that of the patients concerned in this series.

Amongst my colleagues who are equally satisfied with the end-results of total colectomy and ileo-rectal anastomosis is our physician at the Gordon Hospital under whose care come all cases of ulcerative colitis. One of my critics from Canada, in suggesting that what I have written is misleading and dangerous both to the patient and to the surgeon, qualifies this by stating that the patients we see here may be different from those seen in his country. I do not think that they are different—indeed some of our cases have come to us from across the Atlantic and the excised colons are very typical specimens of the complaint. I think that the real reason for the difference between our results and those of others who have attempted to cure the disease by colectomy followed by restoration of continuity of the bowel is that the anastomosis in our cases has been carried out to the rectum and not to the colon as has so often been done in other series. In fact I know of no report, apart from those from the Gordon Hospital, in which the necessity of anastomosing the ileum to the rectum and not to the colon has been stressed.

Most pathologists and most clinicians who have examined many of these cases will agree that the pelvic colon is usually the site of the most advanced changes associated with the

disease. Here ulceration of the mucosa is most prominent, here crypt abscesses are abundant, and here accumulations of polymorphs and lymphocytes are most marked. Moreover the operative appearances of inflammation, the sodden bowel wall and peri-colitis are usually most obvious in this part of the large intestine. I think therefore that if the resection retains a part of the pelvic colon and if the anastomosis is made between this and the ileum then a large proportion of cases will fail to improve as a considerable length of the most diseased bowel remains. There is no doubt that even with this treatment some of the cases will improve remarkably as has been reported by Devine and Corbett. But because of the retention of so much diseased bowel the majority will not, and I think that it is in part because of the disappointment with these cases that the advocacy of a permanent ileostomy coupled with ablation of the whole of the large intestine including the rectum has come to be accepted.

A case, perhaps, could be made for a permanent ileostomy and total excision of the large intestine as the method of choice in the surgical treatment of ulcerative colitis if it could be shown that the rectum remaining after a conservative operation showed no signs of healing and that its continued presence was the cause of persistence of the primary or secondary symptoms of the disease. This argument has certainly been used by those opposed to the methods of treatment that I advocate. Nevertheless in my experience when the whole of the colon is removed and ileo-rectal anastomosis performed, the subsequent improvement of the patient's condition is accompanied by a corresponding resolution of the inflammatory changes in the rectum. It is as if once the patient's general condition returns to normal as a result of the extirpation of the vast bulk of the disease he is then able to combat the residual infection in the rectum. I do not mean by this that the rectum returns absolutely to its pre-inflammatory state. Its walls have been diffusely inflamed, the complicated architecture of its crypts destroyed and its muscular coat often in part replaced by fibrosis. A complete return to a normal soft distensible structure could not be expected. But it does resolve into a structure in which, although the healing by fibrosis in its wall renders it less capable of distension, the inflammation has subsided. Moreover, although the exact normal mucosal architecture is lost the underlying scarred wall does become covered by a mucosa very similar to that existing before the onset of the disease.

I believe that many of us have a very wrong impression with regard to the pathology of this condition as so often the ulcerative process that occurs is considered as an irreversible one. That certainly in the cases of ileo-rectal anastomosis which I will show is not a true concept and I am sure that provided residual islands of mucosa have survived the ravages of the complaint they can regenerate and produce a new lining to the bowel. This regeneration undoubtedly also occurs in the case which recovers as the result of medical treatment. Most surgeons will have sigmoidoscoped these patients before and after such a regime and surely must sometimes have been amazed at the complete disappearance of the ulceration that they saw on the first examination. Pseudopolypi, too, may disappear and this is understandable as they are but residual islands of mucosa which, with the re-epithelialization of the bowel wall, lose their separate identity. Figs. 1–4 illustrate the regeneration occurring in cases under medical and surgical treatment, as revealed by biopsies removed from the rectum.

All of what I have said and the sections which I have shown support, I think, the view that I have of this disease which is that provided the patient can overcome the toxæmia associated with the condition—and in the chronic as well as in the acute case it and all its associated manifestations are severe—the disease will resolve. The part that surgery has to play in those cases requiring surgery for their cure is to help the patient overcome this toxæmia. This it can well do by removing the bulk of the cause of the toxæmia—that is by total colectomy but with retention of the rectum. With the rapid improvement of the patient's general condition which follows such an excision the inflammatory changes in the rectum resolve, so that it is perfectly able to carry on its normal function. Its excision with the institution of a permanent ileostomy therefore becomes unnecessary.

Again a case could be made for excision of the large intestine and the formation of a permanent ileostomy if it could be shown that the establishment of an anastomosis between the ileum and the rectum affected by the disease was a dangerous operation as has been suggested. Now I am not for one minute pretending that these cases are anything but the most difficult to look after. In the post-operative period such complications as ileus, intestinal obstruction, fluid and electrolyte disturbances and occasionally leakage from the anastomotic line may occur and in the severely toxic and often desperately ill patient there is little margin between life and death. Each complication therefore needs to be recognized at its early onset so that it may be combated and corrected immediately.

Nevertheless with a team especially interested and trained to deal with this condition—and I would like to pay tribute here to my anæsthetist Dr. C. B. Lewis, my registrars and housemen at the Gordon Hospital and to our sisters and nurses there, all of whom have contributed

largely to any success that I may have achieved—the mortality between operation and final recovery is low. Of 38 cases in my own personal series the results of which are summarized in Table I, one has been lost.

TABLE I.—SUMMARY OF RESULTS (1952–1956) OF TOTAL COLECTOMY WITH ILEO-RECTAL ANASTOMOSIS

Number of cases 38. Operative death 1. (Mortality rate under 3%.)
Excluding 4 convalescent cases and 1 with liver failure, all are in good health and, with 1 exception, are fully engaged in their former occupations.
Average number of bowel actions: Day 5–6. Night 0–1.
Weight increase: Of 32 patients in whom treatment has been completed, 29 now weigh as much or more than their previous maximum weight.
Complications: Two intestinal obstructions (one included in convalescent cases). Both recovered after operation.
One leaking anastomosis.

The more I see of these cases the more I consider that in the acute case and invariably in the fulminating type it is safest to perform the operation in two stages. The initial stage consists of a colectomy with the formation of an ileostomy, exteriorizing the upper open end of the rectum. The ileum and the rectum are brought out close together through the lowermost part of the paramedian incision thus rendering the subsequent hook-up a simple matter.

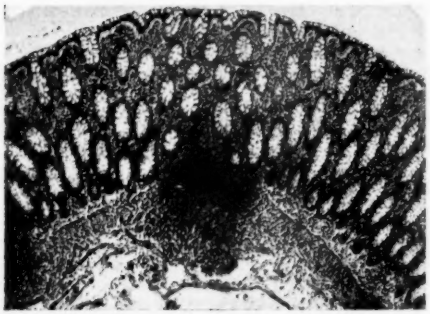


FIG. 1.—Biopsy appearances of a normal rectum. × 36.

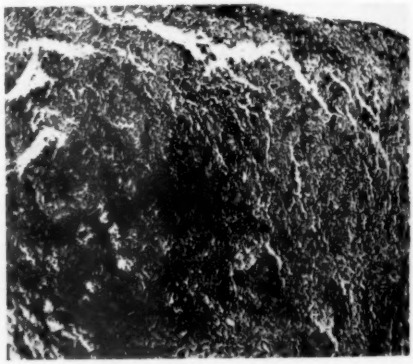


FIG. 2.—Pre-operative rectal biopsy from a case of ulcerative colitis. × 30.

FIG. 3.—Post-operative rectal biopsy from the same case four months after operation. Although the mucosal architecture does not conform to the regimented pattern of the normal complete covering of the ulcerated areas has taken place. × 35.

FIG. 4.—Rectal biopsy showing mucosal regeneration in a case treated successfully by medical methods. × 33.

When I do the operation in one stage I carry out a side-to-side anastomosis of ileum to rectum exteriorizing the upper end of the latter as a proctostomy. It must be appreciated that the rectal wall is friable and inflamed and that sutures may tend to cut out. I have therefore felt that, if a direct anastomosis between the ends of the ileum and rectum is carried out, any rise in tension in the rectum the result of gaseous or fæcal accumulation might well cause disruption of the anastomotic line. If the open end of the rectum is exteriorized any rise in pressure cannot occur as fæces or gas will discharge through this. The safety valve as I have called it may close naturally but may require operation to effect final closure. Figs. 5 and 6 illustrate the operative procedures, and Figs. 7 and 8 a patient treated by this method.

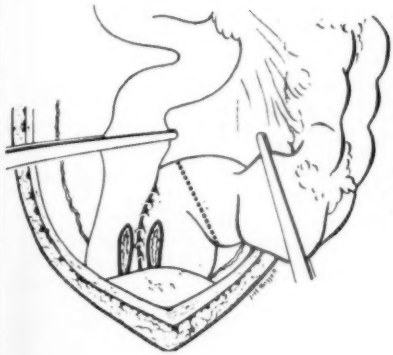


FIG. 5.

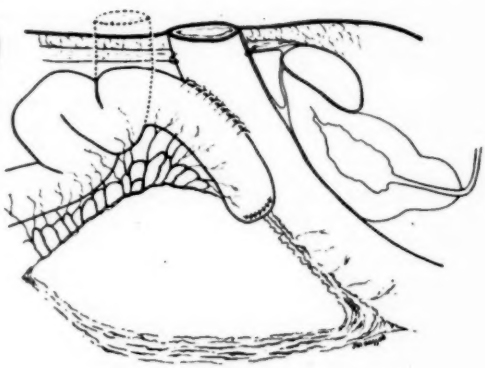


FIG. 6.

FIGS. 5 and 6.—Diagrams to show one-stage ileo-rectal anastomosis, the upper end of the rectum being brought out on to the surface of the abdomen. The residual space between rectum, ileum and posterior abdominal wall is subsequently obliterated to prevent post-operative obstruction. The dotted line (Fig. 6) indicates the temporary ileostomy formed in a two-stage operation.

FIG. 7.

FIG. 8.

FIGS. 7 and 8.—Pre- and post-operative photographs of a patient so treated.

Finally in this argument of retaining the rectum in the surgery of ulcerative colitis I would say that should the operation prove a failure—and in none of our series has such been the case—the rectum can still be removed and an ileostomy performed without subjecting the patient to any additional major operative procedure than would have been the case if this had been carried out as part of the initial planned treatment. Surely it is worth giving the patient a chance to preserve a normal route of evacuation rather than at once subjecting him or her to the appalling inevitability of excision of the rectum.

[*June* 15, 1956]

MEETING AT BRISTOL ROYAL INFIRMARY

Anal Fissure in Pædiatric Practice

By JOHN APLEY, M.D., M.R.C.P.

ON looking through standard books and descriptions, a pædiatrician is astonished to find it stated that children—if mentioned at all—very rarely suffer from anal fissure.

In fact, anal fissure is one of the common disorders in pædiatric practice (Apley, 1954), and it would be recognized still more commonly if the simple method of diagnosis by direct inspection was more widely appreciated and practised. The lesion is found throughout the childhood years, though it is commonest in infancy. I infer that children are rarely referred to proctologists, possibly because of the ways in which fissure-in-ano presents in early life.

In the *acute phase* there is in most cases a sudden onset of pain on defæcation. Sometimes there is an abrupt unwillingness on the part of the child to sit or walk, or very occasionally to micturate. In the *chronic phase* the common complaint is of chronic constipation, often with various permutations and combinations between spurious diarrhœa, recurrent abdominal pain, vomiting and abdominal distension.

The *onset* can nearly always be dated back to a febrile illness, in which a period of dehydration and consequent constipation is followed by the passage of a hard, painful stool which may be tinged with blood. Occasionally in young infants there is instead an initial gastro-enteritis.

The *diagnosis* may be suspected from the history of the sudden onset, reinforced by observing marked contraction of the peri-anal muscles when examination is attempted, and confirmed simply by visualization of the fissure. In children even more than adults examination must be gentle. With the fingers the anal orifice is progressively opened up to view under a good light. Insertion of a finger or an instrument is unnecessary; it is also harmful, since it causes pain which antagonizes the child and parents and makes them unco-operative as regards treatment.

I have found *medical treatment* completely successful in the very large majority of children. These results have surprised some surgical colleagues, whose patients are nearly all adults, and it may well be that there is a different response in the two age-groups. Effective medical treatment is simple. A lubricant (liquid paraffin) is given in small doses by mouth several times daily for a few weeks. In addition, a local anæsthetic is inserted rectally several times daily, and especially just before defæcation is expected, for a period of some two weeks in acute cases and rather longer in chronic ones. I use amethocaine hydrochloride (B.P.) ointment in a non-greasy base, in a strength no greater than 1% to avoid local reactions. It is inserted on a slim pledget of cotton-wool wrapped round an orange-stick. The mother is shown how to carry out the first application in the out-patient clinic, and the child's obvious relief at the loss of pain is a potent factor in ensuring future co-operation. Subsequently the mother continues with the treatment at home. Of course, the success of this sort of domiciliary treatment depends to a great extent on the mother's intelligence. When she is clearly inept the same treatment carried out in hospital is almost invariably successful.

The *results* have been very satisfactory. Of nearly 100 cases treated in the past few years only 3 have been referred for surgical treatment. In about 1 case in 20 in which the condition recurred it was associated with severe constipation; in these cases the fissure responded again to local treatment with amethocaine, and the constipation was treated with liquid paraffin or, more recently, a synthetic "wetting" agent (dioctyl sodium sulphosuccinate) which prevents the formation of hard stools by promoting the retention of water in the fæces.

The *rationale of treatment* is a subject for discussion. Since Thompson's (1899) classic description of the anal sphincters was incorporated into surgical practice by Milligan *et al.* (1937) there have been many changes of opinion regarding the importance (and, indeed, even

the structure) of the internal and external sphincters and their role in the causation and cure of anal fissure (Goligher *et al.*, 1955). In children, at least, evidence for the widely-held view that forced dilatation of the sphincters is essential in treatment seems unconvincing. Under the regime outlined above neither the insertion of the local anæsthetic nor the passage of soft, lubricated stools can produce significant dilatation. Nevertheless a cure is almost invariable. Evidently fibrosis of such a degree that it necessitates forced dilatation or division of the sphincter is unusual in childhood, even in long-standing cases. The old explanation that the abolition of pain is accompanied by relief of spasm, and so permits natural healing, may be an over-simplification, but it seems to account satisfactorily for the observed sequence of events in the fissures of childhood.

My experience of *anal fissure in pædiatric practice* may be briefly summarized:

(1) The lesion is common, though the patients are rarely referred to proctologists.

(2) Apart from constipation, which may become habitual even after a fissure has healed, sequelæ and complications are uncommon. Sentinel tags and granulations sometimes develop, but abscesses and fistulæ are extremely rare.

(3) Healing occurs very readily, and I have observed spontaneous healing. In the very large majority of cases adequate medical treatment produces a cure without any necessity for surgical intervention.

REFERENCES

Apley, J. (1954) *Practitioner*, **172**, 171.

Goligher, J. C., Leacock, A. G., and Brossy, J. J. (1955) *Brit. J. Surg.*, **43**, 51.

Milligan, E. T. C., Morgan, C. N., Jones, L. E., and Officer, R. (1937) *Lancet*, ii, 1119.

Thompson, P. (1899) Myology of the Pelvic Floor. London.

Complete Prolapse of Rectum: Thiersch's Operation

By A. G. McPherson, M.Chir., F.R.C.S.

My interest in Thiersch's operation was stimulated by having to deal with two gross mental defectives in 1950–51 with complete rectal prolapse. I recollected that this operation had been advocated in the aged by Mr. Dickson Wright at a Meeting of the Proctological Section of the Royal Society of Medicine (*Proceedings*, 1949, **42**, 1005) and that, at that same meeting, the results of proctosigmoidoscopy had been shown by Mr. E. S. R. Hughes to be unsatisfactory.

There were two additional cases, a rather simple-minded male, and a tabetic female with Charcot's disease of the hips. In all these cases a simple operation seemed indicated and I performed Thiersch's operation of encircling the anal canal with a silver wire.

Further cases presented and were dealt with in similar fashion, not always with such clear indications, but all with troublesome complete prolapse, and with the addition of 3 cases belonging to my colleague Mr. John Pocock, I now have a small series of cases whose results are reviewed in Table I.

Table I

Thiersch's Operation

Males	3
Females	8
Total	11
Age distribution	28 to 90
Average age, excluding those with mental defect	65

Associated Disease

Gross mental defect	2
"Simple"	1
Depressive psychosis + Addison's disease	1
Tabes dorsalis (with Charcot's hips)	1

There are 11 cases in the series, 3 males and 8 females. The ages ranged from 28 years, a female with Addison's disease and a depressive psychosis, to 90. 2 males were gross mental defectives, 1 female had tabes dorsalis (Table I).

The results are shown in Tables II and III. The 3 males were all apparently cured for five or more years following a single wiring procedure, although the wire is known to be broken in two and assumed to be broken in the third (Table II).

RESULTS OF THIERSCH'S OPERATION

TABLE II

Apparent Cure—No Prolapse Now

(*Males*)

(1) T. H.	(M.D.)	? age	6 years F.U.	Wire broken
(2) C. G.	(M.D.)	? age	6 years F.U.	Wire presumed broken
(3) M. S.	(Simple)	Aged 41	5 years F.U.	Wire broken

Satisfactory Results

(*Females*)

Wire Intact—No Prolapse

(4) M. C.	Age 66	at 18 months
(5) S. S.	Age 28	at 9 months
(6) L. C.	Age 49	at 2 months

Required further wiring

(*Females*)

(7) K. L.	Age 48	Satisfactory for 18 months—wire ulcerated and prolapse recurred Wire replaced—no prolapse at 10 months
(8) E. W.	Age 90	Satisfactory for 7 months—wire broke Wire replaced—satisfactory (recent)

TABLE III

Partially Satisfactory Results

Recurrent Prolapse—Wire Intact

(9) B. F.	Age 65	Tabetic—satisfactory three years, then acute prolapse—wire changed. Satisfactory seven months, recurred—wire reinserted (recent)
(10) A. H.	Aged 58	Satisfactory 9 months Prolapse recurred—? for re-wiring

No Follow-Up

(11) A. H.	Age 83	(recent)

TABLE IV

Complications

Treated by Re-wiring

Early ulceration of wire	2 operations	3 cases
Late ulceration of wire	2 operations	
Acute prolapse through intact wire		2 cases

5 additional cases are regarded as satisfactory, having no prolapse after one or more wirings and 2 cases are regarded as partially satisfactory, as acute prolapse through an intact wire has occurred, after a significant period of satisfactory control (Table III). Case No. 9, the tabetic patient, was controlled for three years and then prolapsed acutely, she prolapsed again seven months after re-wiring, and is at present controlled by a third wire, but she has a very poor perineum which does not improve.

Complications (Table IV) were ulceration of the wire or acute prolapse and have been treated by removal of the wire and re-wiring either immediately or after an interval.

This very simple operation is of great value in selected cases where major surgical intervention is contra-indicated, and may even be worthy of trial in some patients who could in fact tolerate a major procedure.

BOOK REVIEWS

Sir William Arbuthnot Lane, Bt., C.B., M.S. An Enquiry into the Mind and Influence of a Surgeon. By T. B. Layton, D.S.O., M.S. (Pp. viii + 128; illustrated. 21s.) Edinburgh and London: E. & S. Livingstone Ltd. 1956.

William Arbuthnot Lane is to-day little more than a name to the younger generation. To those who have reached retiring age he represents one of the most dramatic figures that ever trod the surgical stage. He was the leader of those who transformed the messy endeavours of Lister's disciples into the Aseptic Surgery of to-day. He revolutionized the treatment of fractures, and established a standard of surgical technique that is the basis of modern orthopædic surgery. He advanced every branch of surgery in which he practised. He was a leader rather than a teacher, a prophet rather than a pedagogue. He was a dreamer, a mystic, one who saw visions and spoke in parables, one who was worshipped with a fanatical devotion by all who were privileged to serve him and regarded with envy, hatred and malice by many of his contemporaries. He wrote little but by his personal influence he moulded the outlook and shaped the careers of more men who themselves became leaders than any figure in surgical history.

To capture such a great spirit on paper is a difficult task. Layton tells us of Lane's family, of his father the Irish Brigade Surgeon, whose journeys with the troops took his wife and young family to all parts of the world. He tells of the formative years, how he worked in the anatomy department far into the night dissecting the skeleton, how he learned decision and manual dexterity during his year as House Surgeon in the Tite Street Children's Hospital in 1882. He tells of the ceaseless struggle for perfection that was the keynote of his character. On the title page he quotes from Æschylus' "Agamemnon": "Alas! Alas! my King, my King. How can I weep for you?" and the whole book exhales that hero-worship that Lane inspired. Layton is one of the many on whom the mantle descended, and he strives to portray to a later generation the majesty of the shoulders from which it fell.

Immunology and Serology. By Philip L. Carpenter. (Pp. viii + 351; illustrated. 45s. 6d.) Philadelphia and London: W. B. Saunders Company. 1956.

The book is based on the author's lecture course in immunology and serology. It is designed to give an outline of the immunity processes with special emphasis on serology. As the author says, more is known of serology. Fundamental principles are emphasized as far as possible and a wide range of references is given, by no means exclusively medical. Both plant and animal kingdoms are included. Not only are the earlier papers of historical interest included but also sufficient recent references to cover the growing points of the subjects. The more recent literature is mainly but not entirely drawn from English-speaking sources. The inclusion in the index of the authors whose papers are referred to facilitates the tracking of papers into the chapter bibliographies. In what may be described as the epistle dedicatory the author gives a condensed account of Plato's "image of the cave" very aptly in relation to the changing concepts in immunology and serology. Although Plato cannot be brought into the ranks of the immunologists, his parable is very much to the point. The book is not a handbook but it supplies a reasonable background for further advanced study. The main subjects are covered in some fourteen chapters and a chapter on experimental methods. All the usual types of reactions are studied including virus immunity and allergy. The historical aspects are shown in relation to present-day views and points of controversy are indicated. No finality of absolute up to dateness is claimed, a wise attitude when dealing with such a growing subject. It is interesting that while the author indicates that, as a result of the study of precipitation reactions, there is now evidence suggesting the non-homogeneity of certain allegedly pure toxins and toxoids, he still accepts Pappenheimer's description of the toxin-antitoxin reaction. However this is perhaps an indication of the state of real knowledge of the subject at present. Whatever the views of experts on points of detail the student should find this book a useful starting point from which to develop his knowledge and come to his own conclusions based on the text and the literature indicated. The book is well produced and the print clear and up to the standard we are accustomed to expect from American textbooks.

The Biochemistry and Physiology of Bone. Edited by Geoffrey H. Bourne, London Hospital Medical College. (Pp. xii + 875; illustrated. $20.00.) London: Academic Books Ltd. (New York: Academic Press.) 1956.

The presentation of any broad survey of current knowledge in most fields of medicine is coming increasingly to take the form of a co-operative effort by a group of experts all of whom are engaged actively in advancing some aspect of the subject. For the more general medical reader, the value of such volumes depends not only on the careful choice of suitable authors, but also importantly on the skill with which their various contributions have been assembled and co-ordinated by the editor. In both respects, the present volume is notable, for Dr. Bourne has brought together a series of authoritative essays in such a way as to provide a remarkably comprehensive account of modern work on the morphology and biochemistry of bone and cartilage. Moreover, its present appearance is opportune, for it is now possible to incorporate with older and classic work the many diversified applications of radioactive isotopes to the study of osteogenesis and calcification that since the war have thrown much new light on these difficult subjects.

The book contains 24 more or less equal chapters. The first 8 are for the most part morphological and deal both with the cytology of bone and cartilage and with the organic and mineral constituents of their intercellular matrices. Admirable chapters have been contributed by Pritchard on the osteoblast and its functions, by Rouiller on collagen fibre formation and by Carlström and Engström on the application of X-ray diffraction techniques to bone structure. Bell has described very interestingly his application of physical and physiological conceptions to the study of "bone as a mechanical engineering problem".

The middle third of the book is mainly biochemical. Bourne himself has chapters on the phosphatases of bone and their histochemical recognition and on the effects of deficiencies of vitamin C on both osseous structures and intercellular substances of tissues in general. The light that the use of radioactive isotopes is shedding on osteogenesis is made very apparent by LeBlond and Greulich's "autoradiographic studies on bone formation and growth". Other chapters in this portion of the book are concerned with citric acid metabolism in bone and with the participation of vitamins A and D and of the steroid hormones in osteogenesis.

The last third of the book is largely concerned with certain physiological and pathological aspects of bones and other skeletal structures. Honor Fell and H. M. Evans give admirable accounts of their well-known studies on osteogenesis *in vitro* and on the regulation of skeletal development by the anterior pituitary gland respectively. Ham discusses repair and transplantation of bone largely from the standpoint of his own experimental studies, while Janet Vaughan reviews the pathological effects of ionizing radiations from the distinctive aspect of skeletal structures.

This book should appeal to a wide and varied circle of readers. Not only does it provide an unequalled survey with comprehensive references for the many investigators now engaged on research on various aspects of the physiology and pathology of skeletal tissues, but it also affords a broad and penetrating survey of the recent advances in this field that should prove of great value to orthopædic and dental surgeons in suggesting fruitful directions for improvements in many practical aspects of these specialties.

The format of the book as regards letterpress, illustrations and binding is excellent, and the literary standards of almost all the contributions is unusually high for publications of this character. Dr. Bourne has shown very convincingly how well such a collaborative monograph can be prepared.

Masked Epilepsy. By Hugh R. E. Wallis, B.A., M.D., M.R.C.P., D.C.H. (Pp. x + 51. 7s.) Edinburgh and London: E. & S. Livingstone Ltd. 1956.

The author of this monograph sets out to show that masked epilepsy in childhood is a much more common condition than is generally realized. He gives an account of 20 children in whom he considers that this diagnosis is justified, basing his opinion upon the paroxysmal nature of the attacks, a family history of epilepsy or masked epilepsy, an abnormal electroencephalogram and a satisfactory response to anti-convulsant drugs. It may be noted in passing that in 3 of the cases cited, the only evidence of epilepsy was the success of treatment with phenobarbitone; the author considers that this proves the diagnosis, a statement which it is hard to accept.

Next follows a chapter describing the different forms in which masked epilepsy may show itself, the list, which is indeed a formidable one, includes cyclical vomiting, recurrent abdominal pain, sweating of the head, night terrors and recurrent pyrexia. In the matter of recurrent abdominal pain the author has a polite dig at those who believe that it is frequently psychological in origin implying that if his hypothesis of masked epilepsy is thought to rest upon an insecure foundation, they are in no better a position.

The monograph, which is clearly written, gives food for thought, but few will be prepared to accept unreservedly some of the conclusions which the author arrives at.

Section of Orthopædics

President—Sir REGINALD WATSON-JONES, M.Ch.Orth., F.R.C.S.

[*June* 9, 1956]

MEETING AT THE NUFFIELD ORTHOPÆDIC CENTRE, OXFORD

Blood Supply of the Epiphyseal Plates of the Rabbit's Tibia

By J. D. MORGAN, F.R.C.S.

Nuffield Orthopædic Centre

BLOOD reaches the epiphyseal plate from three sources. The epiphyseal surface of the plate is supplied by a series of short "loops" which have a brush-like form, as they are arranged in many groups, each consisting of about a dozen loops. The arterial side of the loop is a terminal branch of an epiphyseal artery and the venous side drains into the venous sinusoids of the epiphyseal marrow.

The loops are short and relatively widely spaced and form a regular fringe pointing towards the cartilage plate but separated from it by a calcified area.

These vessels supply the proliferating layer of the epiphyseal cartilage.

The metaphyseal surface of the plate has a much more dense and active arrangement of vessels which lie close together. On this side the "loops" are formed by the terminal branches of the nutrient and accessory nutrient arteries. The loops have a characteristic long, straight form, each reaching exactly to the end cell of a column. The venous side drains into the venous sinusoids of the metaphyseal marrow.

Each loop is normally associated with its own column of cartilage cells and is separated from its neighbours by a thin tube of calcified matrix which probably serves to protect it from damage whilst withstanding the compression forces on the growing plate.

The metaphyseal loops supply the hypertrophic layers of the cartilage plate. They vary in length and density with the activity of the plate.

The third series of vessels are very small. They consist of a number of fine branches which anastomose to form a small vessel which runs round the circumference of the plate and is probably concerned with growth in width of the plate.

Assessment of Ununited Fractures of the Carpal Scaphoid

By J. H. S. SCOTT, F.R.C.S.

The Accident Service, The Radcliffe Infirmary, Oxford

WHILE reviewing 105 consecutive injuries of the carpal scaphoid, 20 patients presented fractures with established non-union, none of whom had been previously diagnosed. The 105 patients reviewed had been treated in a period of thirty months in the Accident Service of the United Oxford Hospitals, Radcliffe Infirmary, Oxford; during the same period approximately 6,000 fresh fractures of all types were accepted for treatment. Scaphoid fractures are therefore not common injuries, but fractures with non-union are a significant part of the problem they present.

With one exception the patients with ununited fractures reported following a second injury. The effects of such an injury are variable and have even been described as disastrous in previously symptom-free wrists (Dwyer, 1949). In planning treatment information on this point is vital. Some guide to the prognosis has been sought by reviewing 18 of these patients two to four years after a second injury. 2 patients had bilateral fractures. On review 10 patients were virtually free of symptoms and of the remainder only 3 had required treatment other than a short time in plaster following the second injury.

The following factors were examined in relation to the development of symptoms:

(1) The severity of the second injury. (2) The patient's occupation. (3) The treatment of the original injury. (4) The age of the patient and of his fracture. (5) The degree of osteoarthritis in the wrist.

(1) *The severity of the second injury.*—17 of the 18 patients reported following further injury to the wrist. All of these had suffered violence of a degree sufficient to fracture a normal scaphoid. On two occasions fractures occurred elsewhere in the wrist. One patient sustained a Bennett's fracture and his wrist became symptomless when that fracture united. Another suffered a fracture of the radial styloid and his symptoms increased after the second injury. Of the 17 patients, 2 said their wrists improved following a second injury, and 2 that deterioration had resulted. The degree of violence therefore gives no guide to progress.

(2) *The patient's occupation.*—A paradoxical relationship appears to exist between the patient's work and his symptoms. A higher proportion of those on heavy work were free of symptoms. The explanation is that those with symptoms gravitate to lighter work. The fact that a patient with an ununited fracture of the scaphoid can do a heavy job does indicate among other things, that he has a high threshold for pain. Such a patient's wrist is unlikely to deteriorate following a further injury.

	Patients	Free of symptoms	With symptoms
(2)	On heavy work	9	2
	On light work	1	6

	Patients	Free of symptoms	With symptoms
(3)	Sought no treatment	9	3
	(with 11 wrists)		
	Sought treatment ..	1	2
	Fractures were missed	—	2
	(One patient developed pain "spontaneously", i.e. not following a second injury.)		

(3) *Treatment of the original injury.*—Information about the treatment of the original injury also seems to give some indication of the patient's pain threshold and from that the prognosis after a further injury.

Those who could tolerate the original injury and not seek treatment could in the main bear the sequelæ of non-union, even after further injury. Those who sought treatment and received inadequate treatment were not similarly equipped to cope with the sequelæ. 2 of these 3 patients have symptoms. 2 patients' scaphoid fractures were missed among more serious injuries and both developed symptoms.

It is interesting to note that 5 patients, with seven fractures, cannot remember how or when they were injured. None appeared to have bipartite scaphoids and the possibility of these being stress fractures could be entertained.

(4) *The age of the patient and of the fracture.*—The age of the patient or of the fracture was of no help in establishing a prognosis:

	No symptoms	With symptoms
Average age of patient	36 years	42 years
Average age of fracture	11 years	10 years

(5) *The degree of osteoarthritis in the wrist.*—The degree of osteoarthritic change in association with non-union, considered alone, is of little assistance as a guide to the future behaviour of that wrist. In fact more patients with osteoarthritis were free of symptoms than had symptoms. For example, the patient with the most disorganized wrist, the result of an unreduced trans-scaphoid peri-lunar fracture dislocation of the wrist of twenty years' duration, was free of symptoms, whereas other patients with little degenerative change had painful wrists.

	Free of symptoms	With symptoms
Wrists with osteoarthritis	10	5
Wrists with *no* osteoarthritis ..	2	3

Summary.—In a series of 105 scaphoid injuries 20 instances of non-union were noted. There were 84 fresh fractures, 60 of the waist, 20 of the tubercle and 4 of the proximal pole. There was one malunited fracture of the waist and one fracture of the waist failed to unite. 18 patients with ununited fractures were reviewed, 17 of these two to four years after a second injury. The factors which might be a guide to prognosis at the time of the second injury were analysed. The occupation of the patient and the treatment of the original injury give some indication of the patient's pain threshold and so indirectly of the prognosis.

The X-ray appearances, the nature of the second injury, the age of the patient and of his fracture are of little prognostic significance.

REFERENCE

DWYER, F. C. (1949) *J. Bone Jt. Surg.*, **31B**, 572.

Pseudarthrosis of the Hip-joint

By R. G. TAYLOR, M.A., M.Ch., F.R.C.S.

The Nuffield Orthopædic Centre, Oxford

IN patients suffering from osteoarthritis of the hip-joint, with its progressive interference in work, recreation, and above all sleep, relief by operation often becomes a matter of necessity. Various operations are available for this purpose. It is the object of this article to describe one of them—pseudarthrosis. This procedure is successful regarding the relief of pain; a remarkable degree of stability is preserved, far more than one would imagine considering the nature and extent of the operation. Moreover, movement is restored both for sitting and for walking, thereby eliminating the excessive strain thrown by a stiff hip on the lumbar spine and the knee-joint.

The operation of pseudarthrosis, as described in this article, was first performed by Girdlestone in 1923 (Girdlestone, 1945). It was a modification of the method advocated by Sir Robert Jones (1921) for ankylosis of the hip-joint, in which the greater trochanter with its attached muscles was attached to the stump of the femoral neck after excision of the head. The term pseudarthrosis of the hip-joint implies, in this paper, excision of the head and neck of the femur, and trimming of the acetabular rim.

Technique of operation.—The anterior, lateral, or posterior approach can be used. It is important to avoid damage to the nerve supply of the muscles round the hip-joint. The anterior and upper rim of the acetabulum should be carefully removed in order to facilitate dislocation of the femoral head, and to avoid bony contact between the femoral stump and the acetabular margin during walking. Neglect of the acetabular bevelling may demand revision of the operation to control the pain on weight-bearing.

It is important here to note that the most important stabilizing muscle is the ilio-psoas (Trueta, 1947).

Post-operative management.—The limb is suspended from a beam in a Thomas' splint with a Pearson knee-flexion attachment, the knee resting in 30 degrees flexion. Traction is maintained throughout the period of splintage. The patient lies flat at night to prevent flexion deformity but sits up freely during the day. Lateral rotation should be avoided; the limb should rest in the neutral position. Two weeks after operation, quadriceps exercises with assisted active flexion and extension of the limb are begun. The Thomas' splint is retained for four weeks, after which it is replaced by Russell traction, using pulleys as advocated by Dommisse and Nangle (1947). This allows for massage, and for graduated active and passive exercises to the hip and knee. After six weeks the patient is encouraged to stand up on the sound leg; a week later he walks in a bucket-top calliper with crutches. Ultimately he learns to walk with one stick held in the opposite hand. He is advised to wear the calliper for the first six months. Most patients prefer to discard it after this period.

Discussion.—Patients classified as having good results gained complete relief from pain and were able to walk with the aid of a stick. 30 degrees of active flexion was regained. Passively there was flexion to 80 degrees abduction and adduction to 30 degrees, medial rotation to 10 degrees and lateral rotation to 30 degrees. This procedure has been used with success in patients with osteoarthritis, ununited fracture of the femoral neck, unreduced fracture dislocation of the hip, and in tuberculous arthritis. In a series of 90 patients with a long follow-up 83 obtained a good result, 7 were poor.

It is undoubtedly the best method available for the treatment of ankylosing spondylitis, bilateral pseudarthrosis giving the best results in these patients.

For failed arthroplasties of the Smith-Petersen or Judet type it is the operation of choice.

Causes of poor results.—In rheumatoid arthritis disappointing results were obtained, as although pain in the hip was relieved, there was inability to walk owing to involvement of other joints. Spur development on the femoral stump which impinged against the acetabulum, a complication which would have been avoided by careful levelling, was a cause of persistent pain. This required operative remodelling of the offending surfaces. Two patients with bilateral osteoarthritis who had arthrodeses of one hip and pseudarthroses on the other subsequently developed stress-fractures in the subtrochanteric region on the side of the arthrodesis. In each satisfactory union occurred, and both patients were able to walk with sticks. In one of the earlier cases the head of the femur was left in the acetabulum; this led to ankylosis. Strict adherence to proper operative technique would have prevented such a result. One patient so obese that post-operative management was difficult and satisfactory fitting of a calliper impossible, had a residual lateral rotation deformity and poor function. It is possible that adequate post-operative traction using a Steinmann's

pin might have prevented this. Another patient, a man of 57, was disappointed in not being able to play games after the operation, although he was able to walk with the aid of a stick and was relieved of pain. The scope and nature of this operation is to relieve pain, and to restore mobility and limited function.

Summary.—(1) Pseudarthrosis is the operation of choice in failed arthroplasties of the Judet or Smith-Petersen types.

(2) It is the best method available for the treatment of ankylosing spondylitis.

(3) It is the most satisfactory and reliable operation for patients over the age of 65 years, with disabling osteoarthritis.

BIBLIOGRAPHY

DOMMISSE, G. F., and NANGLE, E. J. (1947) *Brit. J. Surg.*, **34**, 395.
GIRDLESTONE, G. R. (1945) *Proc. R. Soc. Med.*, **38**, 363.
JONES, ROBERT (1921) Orthopædic Surgery of Injuries. London.
MCMURRAY, T. P. (1935) *Brit. J. Surg.*, **22**, 716.
SMITH-PETERSEN, N. M. (1936) *J. Bone Jt. Surg.*, **18**, 869.
TAYLOR, R. G. (1950) *J. Bone Jt. Surg.*, **32B**, 161.
TRUETA, J. (1947) Personal Communication.

Drilling of the Osteoarthritic Hip

By J. AGERHOLM-CHRISTENSEN, D.M.Copenhagen, and J. R. W. GLEAVE, B.M., B.Ch.
Nuffield Orthopædic Centre, Oxford

IN the treatment of the osteoarthritic hip most patients would be satisfied if they could be relieved from the pain which keeps them awake at night and reduces their activity during the day. Therefore, any minor procedure which might give the desired relief is worth trying before embarking on a major operation.

Drilling, or forage, has been known as a pain-relieving procedure for more than twenty-five years. It appears to have been introduced by Graber-Duvernay, who claimed to have achieved relief from pain in 60% of 23 cases. Henderson and Pollock (1940) improved 12 out of 25 cases. Lidström (1936) stated that 41 out of 43 cases were relieved. This very optimistic report is obviously based on a rather premature review, as most patients improved during the early months.

The biggest and most comprehensive review is the Copenhagen series (Bogason, 1952). Berntsen (1937), who introduced forage in Copenhagen, had previously published earlier results. Their material consisted of 105 patients, with 110 hips involved, followed from six to fifteen years.

Their results confirmed those of the previous smaller series, that more than 50% were relieved from pain.

However, it must be pointed out that their material received other treatment in addition to the drilling.

One of us (J. A. C.) decided, therefore, to collect experience of the effect of the drilling only.

Drilling was offered to the patient as a small operation, practically without risk, necessitating only a short stay in hospital. It was explained carefully that it offered about a 50% chance of relief from pain. This meant that some would be free from pain, some would have much less pain and be able to sleep at night and carry out their daily tasks and the remainder would have no benefit, but no deterioration would occur.

It was also emphasized that it was, first of all, a pain-relieving procedure; although some patients got more mobility and strength, this improvement was more uncertain.

It was explained to the patients that as we wanted to know the results of the drilling and the drilling only, no other treatment would be applied. Most of the patients agreed to this suggestion, but a few of them did not give the drilling a fair chance, for soon after the drilling they asked for an arthroplasty.

We decided to use a number of fine drill holes instead of a single larger one for three reasons. Firstly, we planned to drill *through* the joint, having passed through the trochanter neck and head up into the acetabulum, as the osteoarthritic changes are also there. Secondly, if cysts were seen on X-ray, an attempt was made to hit them, otherwise the guide-wires were directed towards the weightbearing area. Thirdly, it had been reported that a larger hole had weakened the structure so much that a fracture had occurred post-operatively.

Post-operatively the patients were allowed free in bed and were encouraged to move about straight away. When they felt fit, they were allowed up and discharged home, but not before an X-ray had been taken to exclude fractures.

We have now done more than 125 drillings here with no deaths and no fractures.

In the first 30 cases, the technique already described has been followed. Later, changes were made in the hope of making improvements.

In order to get an unbiased assessment the review was carried out by the other of us (J. R. W. G.), who saw most of the patients. A few of the cases were seen by other colleagues.

On these occasions, as at other visits to the clinic, it was emphasized to the patient that we wanted only the hard facts regarding the results, and that so far as pain itself was concerned, he was the only one who could give us the information. As we all know, sometimes it is impossible to establish the *origin* of the pain. Great care was taken to analyse the pain. In one case, an acrylic arthroplasty was performed soon after the drilling, as some pain still remained. The pain persisted after the acrylic arthroplasty and no nerve block could remove it.

Anyhow, had the pain disappeared following the drilling alone, it would not be unreasonable to give credit to the drilling for the improvement gained.

The material consists of 13 men, 17 women, with an average age of 55 years.

More than 50% of the cases have benefited from the drilling.

The results seem better than the Copenhagen material, most probably because of the early ambulation.

For various reasons drilling has not been generally adopted.

First of all, with roughly 50% chance of relief of pain, a small series—for example: 10 cases—may easily not show such good results; of the first six hips drilled here, only one was relieved. No doubt a number of surgeons have been discouraged when this has happened.

We speak only about relief of pain: we do not promise freedom from pain; some are free, others considerably relieved. In this way, neither the patient nor the surgeon expects too much. It has been emphasized that the operation may not improve the mobility although there is a considerable increase of movement in a number of cases. Furthermore, we drill both the weightbearing areas, not just the neck of femur but the acetabulum as well. The early movement and weightbearing seem to be an advantage.

It has been thought that the effects are due to an interference with the blood supply, namely re-vascularization. The fact that most patients are relieved immediately rules out this explanation. We suggest that the effect is a sort of drainage or decompression.

We have seen drill holes patent for many months and we believe that the early activity, together with weightbearing, play an important part in keeping the drill holes open.

A further report is being prepared.

It is reasonable to expect better results in earlier cases, where there are few changes, but, on the other hand, we have seen successful drillings when X-rays have shown very severe osteoarthritic changes. We have not been able to forecast when the drilling would work on either clinical or radiological grounds, but we feel it is reasonable to offer the patient drilling as first choice, unless stiffness or faulty position indicates some other procedure.

REFERENCES

BERNTSEN, A. (1937) *Acta Chir. scand.*, **80**, 82.
BOGASON, B. (1952) *Acta Orthop. scand.*, **22**, 153.
HENDERSON, M. S., and POLLOCK, G. A. (1940) *J. Bone Jt. Surg.*, **22**, 923.
LIDSTRÖM, F. (1936) *Nord. med. Tidskr.*, **11**, 181.

Structural Deformities of the Outer Third of the Adult Tarsal Navicular

By WILLIAM WAUGH, M.Chir., F.R.C.S.

Nuffield Orthopædic Centre, Oxford

STRUCTURAL deformities of the outer third of the adult tarsal navicular are probably not so uncommon as has been generally supposed. The first case was recorded by Müller in 1927. Other papers, each reporting one or two examples, followed shortly after this (Weiss, 1929; Simons, 1930; Wilke, 1930; and Frosch, 1931). Apart from Brailsford's (1935, 1939 and 1948) contributions, no other references to the condition have been found in the English literature.

The present paper is based on a study of 8 patients. Two basic types of abnormality, the split outer third (3 cases) and the crushed outer third (5 cases), which have not previously been defined, are recognized (Fig. 1). In either case the large medial fragment may appear to be subluxated around the head of the talus. Each type may be unilateral or bilateral, and may occur in men or women. The onset of pain, which is usually mild, is in early adult or middle life. The youngest patient recorded with this abnormality was 15 years old (Müller, 1927).

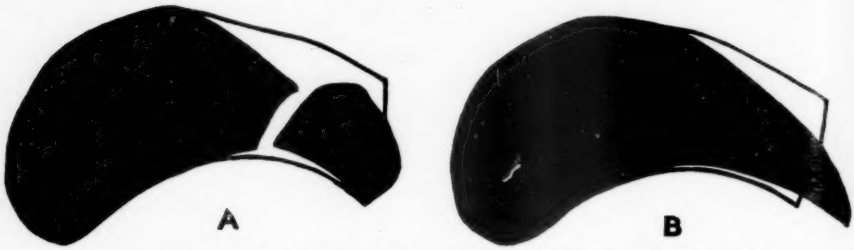


FIG. 1.—Diagram showing (A) the split outer third and (B) the crushed outer third type of deformity.

The feet are flat and rather stiff: the tuberosity of the navicular is prominent. Radiographs of the split outer third type show an abnormal parallelism between the long axis of the talus and os calcis, suggesting that the talus has swung laterally towards the gap in the navicular rather than the medial fragment of the navicular subluxating around the head of the talus. Secondary osteoarthritic changes may be present to a greater or lesser degree.

As far as treatment is concerned, the symptoms associated with either abnormality have been successfully relieved by conservative means, so there has been no opportunity to examine the condition at operation.

The ætiology of these deformities is not clear since very little direct evidence is available. Tomography has been used to give additional information about the nature of the changes, but it will be difficult to provide a convincing explanation until a large series of cases has been studied. There are three main possibilities to be examined.

First, the split outer third may be considered to be a congenital bipartite navicular; the bone either developing from two nuclei which remain separate, or from the migration of an accessory cuboid (Licht, 1941). In 2 cases described by Zimmer (1938) the small lateral fragment was removed and showed normal bone with no evidence of fracture. Radiographically, the criteria for bipartition are debatable (O'Rahilly, 1953); but if the argument is to be upheld the bipartition must be explained phylogenetically on the basis of histo-embryological animal investigations and the primitive tetrapod foot (Trolle, 1948). Trolle has carried out most careful studies and concludes that the requirements for a congenital bipartite navicular are: the two parts should be situated side by side and be approximately equal in size, that together they should form a normal navicular and finally that the division is on a level with the middle of the tibial cuneiform. These conditions are not fulfilled in any of the cases on the present group or in those which have been illustrated in the literature.

Secondly, it might be suggested that these adult deformities occur as a result of a failure of revascularization and reossification of the bony nucleus after Köhler's disease, particularly when the foot has not been protected during the active phase. There is little direct evidence to support this theory: in fact it has only been possible to find one definite case which showed a deformity of the navicular in adolescence (Brailsford, 1939). Karp (1937), King (1935) and others have remarked on the curiously complete restoration of the bone to normal. It is particularly difficult to get a long follow-up since after ten or so years what was a relatively trivial complaint is forgotten and the response to attend hospital for review is poor. However, it has been possible to see 12 patients at an average time of thirteen years from diagnosis and they all have normal naviculars.

It seems reasonable to deduce, therefore, that these changes may be the result of injury to the adolescent or adult bone. This view is supported by Brailsford (1948) after his experience of 20 cases of the split outer third type which he calls osteochondritis of the adult tarsal navicular. Transverse fractures of the navicular are well known: the bone being divided horizontally into a large dorsal and small plantar fragment, the former being dislocated upwards. However, medial subluxation with crushing of the outer third and isolated fractures of this part of the bone have been seen. In the adult deformities which have been described, there may or may not be a history of injury which may or may not be considered relevant. If a crack fracture occurs in the outer third of the bone non-union may result because of the pattern of the local arterial supply (Fig. 2), lack of immobilization and the presence of synovial fluid on either side of the bone. It is also possible that the split could be produced by an abnormal and long-continued strain: in fact this might be a stress fracture. Certainly, the outer third of the navicular is subject to maximum forces of weight bearing (Fig. 3) and this is increased when the foot collapses into valgus.

The traumatic basis for the crushed outer third is perhaps easier to accept and an analogy

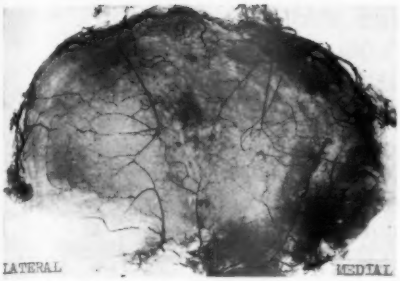


FIG. 2.—Fine grain radiograph of a whole adult navicular after injection with micropaque. The two small lateral arteries and their poor communication with the central vessels are seen.

FIG. 3.—Slab radiograph of a thick horizontal section through the middle of the navicular. The greatest concentration of longitudinal trabeculæ is in the outer third of the bone.

FIG. 4.—Tomograph showing the detailed structure of the crushed outer third in a man aged 46 years. There appears to be a fracture present.

can be drawn between it and Kienböcks disease. The detailed structure is shown in a tomograph of one case (Fig. 4). This suggests that there may be a fracture through the crushed segment. The normal navicular has an abundant vascularization (Fig. 2), but the outer third is the least well-supplied part, its two arteries having a relatively poor communication with the dorsal and plantar groups of central arteries. It seems likely, therefore, that the changes result from ischæmia following damage to these two small vessels. This lesion might occur outside the bone in a soft tissue injury with secondary infraction or in association with a compression type of fracture.

Summary.—(1) Two types of structural abnormality of the adult tarsal navicular are described: the split and the crushed outer third.

(2) Possible ætiological factors are discussed: it being suggested that trauma is the most likely cause of the deformities.

My thanks are due to Professor Trueta for his help and encouragement and also to other members of the staff of the Nuffield Orthopædic Centre, Oxford, for allowing me to study their cases.

REFERENCES

BRAILSFORD, J. F. (1935) *Brit. J. Radiol.*, **8**, 87.
—— (1939) *J. Bone Jt. Surg.*, **21**, 111.
—— (1948) The Radiology of Bone and Joints, p. 152. London.
FROSCH, L. (1931) *Dtsch. Z. Chir.*, **232**, 487.
KARP, M. G. (1937) *J. Bone Jt. Surg.*, **19**, 84.
KING, E. J. S. (1935) Localised Rarefying Condition of Bone. London.
LICHT, E. (1941) *Acta radiol., Stockh.*, **22**, 377.
MÜLLER, W. (1927) *Dtsch. Z. Chir.*, **201**, 84.
O'RAHILLY, R. (1953) *J. Bone Jt. Surg.*, **35A**, 626.
SIMONS, B. (1930) *Z. Orthop. Chir.*, **52**, 564.
TROLLE, D. (1948) Accessory Bones of the Human Foot. Copenhagen.
WEISS, K. (1929) *Fortschr. Röntgenstr.*, **40**, 63.
WILKE, A. (1930) *Röntgenpraxis*, **2**, 751.
ZIMMER, E. A. (1938) *Arch. orthop., Unfallchir.*, **38**, 396.

BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

[*Continued from p.* 936]

'Espinasse (M.). Robert Hooke. pp. 192. London: Heinemann. 1956.

Estripeaut (R.). Considération sur la métamorphose morphologique et physiologique de la cellule humaine. pp. 123. Paris: Maloine. 1942.

Estripeaut (R.). Pathogénie du cancer et néoplasmogenèse. pp. 32. Paris: Maloine. 1943.

Fenichel (O.). Hysterien und Zwangsneurosen. pp. 193. Vienna: Internationaler Psychoanalytischer Verlag. 1931.

Ferenczi (S.), and Rank (O.). Entwicklungsziele der Psychoanalyse: zur Wechselbeziehung von Theorie und Praxis. pp. 67. Leipzig, Vienna and Zurich: Internationaler Psychoanalytischer Verlag. 1924.

Fiessinger (N.). Endocrinologie. pp. 156. Paris: Masson. 1940.

Fiessinger (N.), Olivier (H.-R.), and Herbain (M.). Les diagnostics biologiques. 5th edit. pp. 857. Paris: Maloine. 1944.

Florence (G.). Précis de chimie biologique et médicale. pp. 1200. Paris: Maloine. 1944.

Freud (S.). Totem und Tabu. pp. 216. Leipzig: Internationaler Psychoanalytischer Verlag. 1922.

Fry (Sir William Kelsey), and Ward (T. G.). The dental treatment of maxillo-facial injuries. 2nd edit. pp. 372. Oxford: Blackwell. 47s. 6d. 1956.

Garcin (R.), and Guillaume (J.). Traitement des blessures et des lésions traumatiques cranio-cérébrales récentes. pp. 168. Paris: Masson. 1942.

Griffiths (D. L.), Seddon (H. J.), and Roaf (R.). Pott's paraplegia. pp. 129. London, New York and Toronto: Oxford University Press. 50s. 0d. 1956.

Hess (W. J.). Hypothalamus und Thalamus: Experimentaldokumente. pp. 70. Stuttgart: Thieme. 1956.

Irving (F. A.). The environmental approach to the prevention of poliomyelitis. pp. 16. Privately printed. 4s. 6d. 1956.

Jeanneney (G.). Applications chirurgicales de l'anatomie topographique. pp. 256. Paris: Doin. 1944.

Jeanneney (G.), and Ringenbach (G.). Traité de la transfusion sanguine. pp. 386. Paris: Masson. 1940.

Jones (E.). Sigmund Freud: four centenary addresses. pp. 150. New York: Basic Bks. 18s. 0d. 1956.

Klein (M.). Die Psychoanalyse des Kindes. pp. 324. Vienna: Internationaler Psychoanalytischer Verlag. 1932.

Kopaczewski (W.). Lavoisier et la chimie. pp. 79. Rabat: École du Livre. 1944.

Koressios (N. T.). Recherches psychothérapeutiques sur la dépression nerveuse. pp. 246. Paris: Maloine. 1942.

Koressios (N. T.). Recherches psychothérapeutiques sur les délires. pp. 373. Paris: Maloine. 1943.

Lassance (V.). Hypertension artérielle. pp. 308. Paris: Maloine. 1931.

Lapipe (M.), and Rondepierre (J.). Contribution à l'étude physique, physiologique et clinique de l'électro-choc. pp. 188. Paris: Maloine. 1942.

Laubry (C.). Appareil circulatoire. 2nd edit. pp. 208. Paris: Masson. 1941.

Lavedan (J.). L'action des radiations sur la cellule normale. pp. 128. Paris: Gauthier-Villars. 1945.

Manasse (P.), ed. Handbuch der pathologischen Anatomie des menschlichen Ohres. 2 vols. Wiesbaden: Bergmann. 1917.

Merklen (P.), and Waitz (R.). Atlas d'hématologie. pp. 230. Paris: Maloine. 1942.

Neufeld (J.). Dostojewski: Skizze zu seiner Psychoanalyse. pp. 93. Leipzig, Vienna, Zurich: Internationaler Psychoanalytischer Verlag. 1923.